Bulletin de veille
Perturbateurs Endocriniens
N°27- Septembre-Octobre 2024

Objectif : cette veille bibliographique à pour objectif la surveillance de l'actualité et de la littérature scientifique sur les perturbateurs endocriniens. Cette veille est axée sur les aspects suivants : l'exposition, la toxicité, l'évaluation, la prévention, l'épidémiologie et l'actualité.

La validation des informations fournies (exactitude, fiabilité, pertinence par rapport aux principes de prévention, etc.) est du ressort des auteurs des articles signalés dans la veille. Les informations ne sont pas le reflet de la position de l'INRS.

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Exposition professionnelle

End-of-life vehicle dismantling activity emits large quantities of phthalates and their alternatives: New insights on environmental sources and co-exposure risks.
Shi Y, Zhao L, Zheng J, Ding R, Li K, Zhao H, et al. *Environ Int*. 2024 Aug;190:108933.

Automotive interiors have been identified as significant sources of various chemicals, yet their occupational hazards for end-of-life vehicle (ELV) dismantlers remain poorly characterized. Herein, eight classes of plasticizers, including 11 phthalates esters (PAEs) and 16 non-phthalates esters (NPAEs), were detected in dust samples from inside and outside ELV dismantling workshops. Moreover, indoor dust from ordinary households and university dormitories was compared. The indoor dust from the ELV dismantling workshops contained the highest concentrations of plasticizers (median: 594 μg/g), followed by ordinary households (296 μg/g), university dormitories (186 μg/g), and outdoor dust (157 μg/g). PAEs remained the dominant plasticizers, averaging 11.7-fold higher than their NPAE alternatives. Specifically, diisononyl phthalate and

trioctyl trimellitate were notably elevated in workshop dust, being 15.5 and 4.78 times higher, respectively, than in ordinary household dust, potentially indicating their association with ELV dismantling activities. The estimated daily intake of occupational ELV dismantling workers was up to five times higher than that of the general population. Moreover, certain dominant NPAEs demonstrated nuclear receptor interference abilities comparable to typical PAEs, suggesting potential toxic effects. This study is the first to demonstrate that ELV dismantling activities contribute to the co-emission of PAEs and NPAEs, posing a substantial risk of exposure to workers, which warrants further investigation.
Lien vers l'article

Cancer du sein : peut-on l'envisager comme une maladie professionnelle ?
Favier A, Mathelin C, Gonzalez M, Uzan C. *Gynecol Obstet Fertil Senol*. 2024 Jul 10.

OBJECTIVE: Breast cancer is the leading cancer in women in terms of incidence and mortality. The literature currently identifies several risk factors, some modifiable and others not. Because of its multifactorial nature, the combination of factors either increases or reduces the risk of cancer. Since 2004, the first commission's rapport of the French National Environmental Health Plan has recognized the significant impact of occupational exposure on the development of breast cancer. However, neither primary nor secondary preventive measures have yet been implemented in work environment. METHOD: Based on available literature, we reviewed current knowledge of breast cancer risk factors associated with occupational exposure. RESULTS: The risk factors identified were ionizing radiation, magnetic fields, certain endocrine disruptors, ethylene oxide and night shift work. CONCLUSION: Recognition of breast cancer as an occupational disease is complicated. In some cases, however, it may be possible, particularly in cases of multifactorial exposure. This work should help to raise awareness among employers and reinforce preventive measures in the workplace.
Lien vers l'article

Effects of dioxin exposure on reproductive and thyroid hormone levels and male sexual function in airbase military workers in Vietnam.
Pham The T, Nishijo M, Phan Van M, Nguyen Minh P, Pham Ngoc T, Vu Thi H, et al. *Environ Sci Pollut Res Int*. 2024 Jul;31(35):47644-54.

Dioxins are endocrine disruptors that may disturb male sexual and reproductive function. Studies on human populations are limited, and their results are controversial. This study evaluated the impact of dioxin exposure on reproductive and thyroid hormone levels and sexual function in men. A total of 140 men working in four military airbases (three bases were formerly contaminated with dioxin by the herbicide spraying campaign in the Vietnam War) were recruited to measure the serum dioxin levels. Four reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone (LH), and prolactin) and three thyroid hormones (free triiodothyronine (FT3), free thyroxin (FT4), and thyroid stimulating hormone) were measured. Male sexual function endpoints including sexual drive, erection, ejaculation, problems, and overall satisfaction were assessed by the Brief Male Sexual Function Inventory. The percentage of subjects with low testosterone and LH levels was 19.6% and 16.7%, respectively. Dioxins, especially 2,3,7,8-tetrachlorodibenzo-P-dioxin and toxic equivalent concentrations of polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans, were inversely associated with testosterone and prolactin levels, but positively associated with FT3 and FT4, and showed adverse relationships with sexual function, such as sexual drive, problems, and overall satisfaction. Our results suggested that exposure to dioxin disrupts the homeostasis of reproductive and thyroid hormones leading to adverse effects on male sexual function.
Lien vers l'article

Pesticide exposure and increased breast cancer risk in women population studies.
Panis C, Lemos B. *Sci Total Environ*. 2024 Jul 10;933:172988.

Pesticide exposure is emerging as a risk factor for various human diseases. Breast cancer (BC) is a multifactorial disease with known genetic and non-genetic risk factors. Most BC cases are attibutable to non-genetic risk factors, with a history of adverse environmental exposures playing a significant role. Pesticide exposure can occur at higher levels in female populations participating in rural activities such as spraying of pesticides in the field, unprotected handling of pesticides at home, and washing of contaminated clothes. Exposure can also be significant in the drinking water of certain populations. Here, we reviewed the literature on women's exposure to pesticides and the risk of BC. We summarize the main links between pesticide exposure and BC and discuss the role of dose and exposure context, as well as potential mechanisms of toxicity. Overall, reports reviewed here have documented stronger associations between higher levels of

exposure and BC risk, including documenting direct and acute pesticide exposure in certain female populations. However, discrepancies among studies regarding dose and mode of exposure may result in misunderstandings about the risks posed by pesticide exposure. Plausible mechanisms linking pesticides to breast cancer risk include their impacts as endocrine disruptors, as well as their roles as genotoxic agents, and modulators of the epigenome. Besides establishing links between pesticide exposure and breast cancer, the literature also highlights the critical need to understand the routes and doses of women's exposure to pesticides and the specific associations and mechanisms that are determinants of disease etiology and prognosis.
Lien vers l'article

Nail salon dust reveals alarmingly high photoinitiator levels: Assessing occupational risks.
Shen J, Liu J, Ji X, Liang J, Feng X, Liu X, et al. *J Hazard Mater*. 2024 Aug 15;475:134913.

Photoinitiators (PIs) are chemical additives that generate active substances, such as free radicals to initiate photopolymerization. Traditionally, polymerization has been considered a green technique that seldomly generates contaminants. However, many researches have confirmed toxicity effects of PIs, such as carcinogenicity, cytotoxicity, endocrine disrupting effects. Surprisingly, we found high levels of PIs in indoor dust. Our analysis revealed comparable levels of PIs in dust from printing shops (geometric mean, GM: 1.33 ×10(3) ng/g) and control environments (GM: 874 ng/g), underscoring the widespread presence of PIs across various settings. Alarmingly, in dust samples from nail salons, PIs were detected at total concentrations ranging from 610 to 1.04 × 10(7) ng/g (GM: 1.87 ×10(5) ng/g), significantly exceeding those in the control environments (GM: 1.43 ×10(3) ng/g). Nail salon workers' occupational exposure to PIs through dust ingestion was estimated at 4.86 ng/kg body weight/day. Additionally, an in vitro simulated digestion test suggested that between 10 % and 42 % of PIs present in ingested dust could become bioaccessible to humans. This is the first study to report on PIs in the specific environments of nail salons and printing shops. This study highlights the urgent need for public awareness regarding the potential health risks posed by PIs to occupational workers, marking an important step towards our understanding of environmental pollution caused by PIs.
Lien vers l'article

Epidémiologie

The Association between Maternal Endocrine-Disrupting Chemical Exposure during Pregnancy and the Incidence of Male Urogenital Defects: A Systematic Review and Meta-Analysis,
Albadawi, E. A., Alzaman, N. S., Elhassan, Y. H., Eltahir, H. M., Abouzied, M. M. and Albadrani, M. S., *Metabolites*, Sep 2024, Vol. 14, no. 9.

The increasing incidence of hypospadias and cryptorchidism, coupled with the widespread presence of endocrine-disrupting chemicals (EDCs), has raised concerns about the potential impact of these environmental factors on male urogenital development. This systematic review and meta-analysis aims to evaluate the association between maternal exposure to various EDCs and the risk of hypospadias and cryptorchidism. We conducted a comprehensive search of PubMed, Scopus, Web of Science, and Cochrane databases from inception until May 2024. We included case-control and cohort studies that examined the association between maternal EDC exposure and hypospadias or cryptorchidism, reporting adjusted odds ratios (aOR) or crude odds ratios (cOR). Data were extracted and pooled using a random effects model, and heterogeneity was assessed using the Q test and I-square statistics. The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS). A total of 48 studies were included in the systematic review, with 46 studies included in the meta-analysis. The pooled analysis revealed a significant association between maternal EDC exposure and an increased risk of hypospadias (aOR = 1.26, 95% CI: 1.18-1.35, p < 0.0001) and cryptorchidism (aOR = 1.37, 95% CI: 1.19-1.57, p < 0.001). Subgroup analyses showed that exposure to pesticides, phthalates, alkyl phenolic compounds (ALKs), and heavy metals significantly increased the risk of hypospadias. In contrast, polychlorinated biphenyls (PCBs) did not show a significant association. Significant associations were found with pesticide and PCB exposure for cryptorchidism, but not with phthalate, ALK, or heavy metal exposure. Maternal exposure to certain EDCs is associated with an increased risk of hypospadias and cryptorchidism in male children. These findings underscore the importance of addressing environmental and occupational exposures during pregnancy to mitigate potential risks. Further research is needed to elucidate the mechanisms by which EDCs affect urogenital development and to develop effective interventions to reduce exposure among vulnerable populations. https://doi.org/10.3390/metabo14090477

The mixture of non-persistent endocrine-disrupting chemicals in relation to endometriosis,
Ao, J. J., Zhu, W. T., Jiang, W., Zeng, X. J., Qiu, W., Yin, S. J., Wang, W. J. and Zhang, J., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 286.

Non-persistent endocrine-disrupting chemicals (EDCs) are of significant concern due to their reproductive toxicity. Previous research reported a relationship between a single type of EDCs and endometriosis. Yet, evidence regarding mixed exposure of multiple categories of EDCs is scarce. Between 2014 and 2018, our hospitalbased case-control study recruited 238 endometriosis cases diagnosed by laparoscopy and 296 normal controls in China. Seventeen non-persistent EDCs (phthalates and bisphenols) were measured in urine. The association of single EDC with endometriosis was estimated using logistic regression, while the association between EDC mixture and endometriosis was modeled by Bayesian kernel machine regression (BKMR), quantile-based gcomputation (q-gcomp), and principal component analysis (PCA). Consistent results were observed in both single and mixture models where phthalates and bisphenols were associated with increased risk of endometriosis (mixture effect: adjusted odds ratio (aOR)=1.44, 1.22-1.70) and the major contributors were bisphenol A (BPA) and the metabolites of di(2-ethylhexyl) phthalate (DEHP). Interaction analysis showed that bisphenols exhibited significant synergistic interactions with phthalates. Our results suggest that non-persistent EDCs are associated with endometriosis but the underlying mechanisms remain to be elucidated. Our finding may have important public health implications in preventing endometriosis. https://doi.org/10.1016/j.ecoenv.2024.117129

Prenatal phthalate exposure and pubertal development in 16-year-old daughters: reproductive hormones and number of ovarian follicles,
Assens, M., Frederiksen, H., Pedersen, A. T., Petersen, J. H., Andersson, A. M., Sundberg, K., Jensen, L. N., Curtin, P., Skakkebaek, N. E., Swan, S. H. and Main, K. M., *Human Reproduction*, Oct 2024, Vol. 39, no. 11.

STUDY QUESTION Is there a possible association between prenatal phthalate exposure and late effects in teenage daughters with respect to reproductive hormone levels, uterine volume, and number of ovarian follicles? SUMMARY ANSWER Our study showed subtle associations between phthalate metabolite concentrations in maternal serum from pregnancy or cord blood and LH and insulin-like growth factor 1 (IGF-1) levels as well as uterine volume in their daughters 16 years later. WHAT IS KNOWN ALREADY Endocrine-disrupting environmental chemicals may adversely affect human reproductive health, and many societies have experienced a trend toward earlier puberty and an increasing prevalence of infertility in young couples. The scientific evidence of adverse effects of foetal exposure to a large range of chemicals, including phthalates, on male reproductive health is growing, but very few studies have explored effects on female reproduction. STUDY DESIGN, SIZE, DURATION This follow-up study included 317 teenage daughters who were part of the Copenhagen Mother-Child Cohort, a population-based longitudinal birth cohort of 1210 females born between 1997 and 2002. PARTICIPANTS/MATERIALS, SETTING, METHODS A total of 317 female participants (median age 16 years) were examined for weight, height, and menstrual pattern. A serum sample was analysed for concentrations of reproductive hormones, and trans-abdominal 3D ultrasonography was performed to obtain the number of ovarian follicles, ovarian and uterine size. Prenatal maternal serum samples were available for 115 females, and cord blood samples were available for 118 females. These were analysed for concentrations of 32 phthalate metabolites. Weighted quantile sum regression was used for modelling associations of combined prenatal phthalate exposure with the reproductive outcomes in post-menarcheal females. MAIN RESULTS AND THE ROLE OF CHANCE In bivariate correlation analyses, negative significant associations were found between several prenatal phthalate metabolite concentrations and serum hormone concentrations (testosterone, 17-OH-progesterone, and IGF-1) as well as number of ovarian follicles in puberty. Positive significant correlations were found between prenatal phthalate exposure and FSH and sex hormone-binding globulin concentrations. Combined analyses of phthalate exposure (weighted quantile sums) showed significant negative associations with IGF-1 concentration and uterine volume as well as a significant positive association with LH concentration. LIMITATIONS, REASONS FOR CAUTION Phthalate metabolites were measured in serum from single prenatal maternal blood samples and cord blood samples. Potential concomitant exposure to other endocrine-disrupting environmental chemicals before or after birth was not controlled for. The study population size was limited. WIDER IMPLICATIONS OF THE FINDINGS Our results support the need for further research into possible adverse effects of environmental chemicals during foetal development of the female reproductive system. https://doi.org/10.1093/humrep/deae229

Association between bisphenol A exposure and cardiometabolic outcomes: A longitudinal approach,

Costa, S. A., Severo, M., Lopes, C. and Torres, D., *Journal of Hazardous Materials*, 2024/09/05/ 2024, Vol. 476, p. 135000.

Increased cardiometabolic risk is associated with abnormalities in blood biomarkers profile and adiposity measurements. Some substances found in the food matrix and the environment, called endocrine-disrupting chemicals, may impair cardiometabolic health in the early and later stages of life. Bisphenol A (BPA) is a food contaminant that migrates from food contact materials and may act as an endocrine disruptor, negatively affecting human health. The present work aims to longitudinally assess the association between BPA exposure and cardiometabolic outcomes, considering data from Portuguese population-based birth cohort Generation XXI. Blood insulin (0.06stdβ; 95 %CI:0.03,0.09) and insulin resistance (0.05stdβ; 95 %CI:0.02,0.08) presented a significant longitudinal association with BPA daily exposure after adjustment for important variables and energy. The same findings were observed for fat mass (0.03stdβ; 95 %CI 0.01,0.06) and waist circumference (0.06stdβ; 95 %CI:0.04,0.08). For z-BMI, a significant cross-sectional (0.03stdβ; 95 %CI:0.01,0.04) and longitudinal (0.02stdβ; 95 %CI:0.00,0.04) association was found. This was the first study assessing the association between BPA exposure and health outcomes from childhood to adolescence. We found an association between BPA exposure and increased blood insulin level, insulin resistance, fat mass percentage, waist circumference and z-BMI. Our results point to the need to reduce exposure to BPA in the early stages of life. https://doi.org/https://doi.org/10.1016/j.jhazmat.2024.135000

Associations of prenatal maternal urinary concentrations of triclosan and benzophenone-3 with cognition in 7.5-month-old infants,
Cragoe, N., Sprowles, J., Woodbury, M. L., Musaad, S., Enright, E., Aguiar, A. and Schantz, S. L., *Environmental Research*, Dec 2024, Vol. 263.

Background: Endocrine-disrupting chemicals (EDCs) have been linked to adverse health outcomes and prenatal exposure is known to impact infant and child development. However, few studies have assessed early developmental consequences of prenatal exposure to two common phenolic compounds, benzophenone-3 (BP-3) and triclosan (TCS). Objective: We evaluated the relationship of prenatal exposure to BP-3 and TCS with infant cognition at 7.5 months via performance on a visual recognition memory (VRM) task. Methods: Drawing from the Illinois Kids Development Study (IKIDS) cohort, prenatal exposure to BP-3 and TCS was assessed in pools of five urine samples collected from each woman across pregnancy. Cognition was measured in 310 infants using a VRM task assessing information processing speed, attention, and recognition memory through infrared eye-tracking. Generalized linear regression estimated exposure-outcome associations, followed by stratification to investigate modification of associations by infant sex and stimulus set. Results: Sampled mothers were more likely to be white, college educated, and middle or high income relative to the US population. Mean chemical exposures were significantly higher than those of adult women in the NHANES cohort. In models adjusted for income, gestational age at birth, and testing age, prenatal BP-3 exposure was associated with an increase in run duration (average time spent looking at the stimuli before looking away) (beta = 0.0011, CI-0.0001:0.0022), indicating slower information processing speed, while TCS was associated with significantly longer time to familiarization (time to accrue a total of 20 s of looking time to the stimuli) (beta = 0.0686, CI 0.0203:0.1168, p < 0.01), indicating poorer attention. Stratum-specific analyses isolated both effects to male infants who viewed the second of two stimulus sets. Conclusion: Higher prenatal exposure to triclosan was associated with poorer attention in infancy, while benzophenone-3 may be associated with slower information processing speed, particularly among males. https://doi.org/10.1016/j.envres.2024.119975

Impacts of PFAS Exposure on Neurodevelopment: A Comprehensive Literature Review,
Currie, S. D., Wang, J. S. and Tang, L. L., *Environments*, Sep 2024, Vol. 11, no. 9.

Neurodevelopmental disorders (NDDs) encompass a range of conditions that begin during the developmental stage and cause deficits that lead to disruptions in normal functioning. One class of chemicals that is of increasing concern for neurodevelopmental disorders is made up of per- and polyfluoroalkyl substances (PFAS). In this comprehensive literature review, we investigated data from epidemiological studies to understand the connection between PFAS exposure and neurodevelopmental endpoints such as cognitive function, intelligence (IQ), and memory, along with behavioral changes like Attention-Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD). When we reviewed the findings from individual studies that analyzed PFAS levels in biological samples and their association with NDD, we concluded that there was a correlation between PFAS and neurodevelopmental disorders. The findings suggest that children exposed to higher PFAS levels could potentially have an increased risk of ASD and ADHD along with an

inhibitory effect on IQ. While the results vary from one study to another, there is increasing association between PFAS exposure and neurodevelopmental disorders. Importantly, the findings provide valuable insights into the adverse effects associated with PFAS exposure and neurodevelopment. https://doi.org/10.3390/environments11090188

Association between exposure to perfluoroalkyl substances (PFAS) and endometriosis in the ENDEA case-control study,
De Haro-Romero, T., Peinado, F. M., Vela-Soria, F., Lara-Ramos, A., Fernández-Parra, J., Molina-Lopez, A., Ubiña, A., Ocón, O., Artacho-Cordón, F. and Freire, C., *Science of the Total Environment*, Nov 2024, Vol. 951.

Background: Perfluoroalkyl substances (PFAS) are environmental contaminants present in a wide range of consumer products and frequently detected in drinking water. They have been linked to adverse reproductive health outcomes in women, but there is limited human evidence on the association of PFAS exposure with endometriosis. Objective/Aim: To explore the association between plasma concentrations of several PFAS, considered individually and as a mixture, and the risk of endometriosis in women of childbearing age. Methods: Between 2018 and 2020, 42 patients with endometriosis and 90 controls undergoing abdominal surgery were recruited at two public hospitals in Granada, Spain. The presence or absence of endometriosis was ascertained by laparoscopic inspection of the pelvis and biopsy of suspected lesions (histological diagnosis). Concentrations of 10 PFAS were quantified in plasma samples from participants. Unconditional logistic regression was employed to examine associations of individual PFAS and summed concentrations of short (& sum;SC) and long-chain (& sum;LC) PFAS with odds of endometriosis, and quantile g-computation was used to assess their mixture effect. Results: In models adjusted for age, schooling, and parity, perfluorotridecanoic acid (PFTrDA) was associated with higher odds of endometriosis (odds ratio [OR] = 1.74; 95 % CI = 1.11-2.73 per 2-fold increase in plasma concentrations), while marginally significant associations were found for perfluorohexane sulfonate (PFHxS) (OR = 1.45, 95 % CI = 0.94-2.21) and & sum;SC PFAS (OR = 1.48; 95 % CI = 0.96-2.30). No associations were found for the remaining PFAS. The PFAS mixture was non-significantly associated with 1.7-fold higher odds of endometriosis (95 % CI = 0.73-3.80), with perfluorononanoic acid (PFNA), PFHxS, and PFTrDA being the major contributors to this effect. Conclusions: These findings suggest that exposure to certain PFAS may increase the odds of endometriosis. However, given the modest sample size, further studies are warranted to verify these results. https://doi.org/10.1016/j.scitotenv.2024.175593

Perfluoroalkyl substances exposure and the risk of breast cancer: A nested case-control study in Jinchang Cohort,
Dou, Q., Bai, Y. A., Li, Y. J., Zheng, S., Wang, M. Z., Wang, Z. G., Sun, J. Y., Zhang, D. S., Yin, C., Ma, L., Lu, Y. B., Zhang, L. Z., Chen, R. R. and Cheng, Z. Y., *Environmental Research*, Dec 2024, Vol. 262.

Background: As persistent organic pollutants (POPs), perfluoroalkyl substances (PFAS) may potentially impact human health. Our study aimed to investigate the prospective association between PFAS exposure and the incidence risk of breast cancer in females. Methods: By fully following the Jinchang Cohort after a decade, we conducted this nested case-control study with 135 incidence cases of breast cancer (BC) and 540 bias-paired controls. The PFAS levels were tested by baseline serum samples. Conditional logistic regression and a restricted cubic spline model were employed to investigate the BC incidence risks and the dose-response associated with single PFAS component exposure. Furthermore, the Quantile g-computation model (Qgc), random forest model (RFM), and bayesian kernel machine regression models (BKMR) were integrated to estimate the mixed effects of PFAS exposure on the incidence risk of BC. Results: Exposures to specific PFAS components were positively associated with an increased incidence risk of breast cancer. By grouping the study population into different baseline menopausal statuses, PFHxS, PFNA, PFBA, PFUdA, PFOS, and PFDA demonstrated a similarly positive correlation with BC incidence risks. However, the increased incidence risks of BC associated with PFOA, PFOS, PFUdA, and 9CL-PF3ONS exposure were exclusively found in the premenopausal population. Both BKMR and Qgc revealed that exposure to mixed PFAS was associated with an increased risk of breast cancer, with Qgc specifically indicating an odds ratio (OR) of 2.21 (95% CI: 1.53, 3.19). Random forests showed that PFBA, PFOS, PFHxS, and PFDA emerged as predominant factors potentially influencing breast cancer incidence. Conclusion: Our findings suggest a strong association between PFAS exposure and the incidence of breast cancer. Premenopausal women should exercise more caution regarding PFAS exposure. https://doi.org/10.1016/j.envres.2024.119909

The Study of Environmental Exposure of Mothers and Infants Impacted by Large-Scale Agriculture (SEMILLA): Description of the Aims and Methods of a Community-Based Birth Cohort Study,

Handal, A. J., Orozco, F., Montenegro, S., Cadena, N., Muñoz, F., Del Rio, E. R. and Kaciroti, N., *Children-Basel*, Sep 2024, Vol. 11, no. 9.

Background/Objectives: Women of childbearing age not only reside in agricultural communities but also form an integral part of the agricultural labor force. Limited research investigates the impact of prenatal fungicide exposure on infant health, specifically ethylenebisdithiocarbamates and their toxic by-product, ethylenethiourea (ETU), particularly in occupational settings. This paper describes the background, aims, protocol, and baseline sample characteristics for the SEMILLA study, which investigates prenatal ETU exposure, neonatal thyroid function, infant growth, and neurobehavioral development in an agricultural region of Ecuador. Methods: This cohort study follows pregnant women and their infants up to 18 months of age, incorporating urinary biomarkers and survey data on ETU exposure and infant growth and neurodevelopmental measures. Data collection includes detailed questionnaires, scales, and physical examinations on maternal and infant health and development, as well as environmental factors. Descriptive statistics on key characteristics of the study population at baseline are presented. Results: SEMILLA enrolled 409 participants (72% enrollment rate): 111 agricultural workers (mostly floricultural), 149 non-agricultural workers, and 149 non-workers. Baseline characteristics show comparability between work sector groups, with some economic differences. Conclusions: SEMILLA will provide key evidence on prenatal fungicide exposure and infant development and encompass comprehensive multistage data collection procedures in pregnancy and infancy, focusing on structural and social determinants of health as well as individual-level chemical exposures. The community-based approach has proven essential, even amid challenges like the COVID-19 pandemic. The medium-term objective is to inform sustainable interventions promoting maternal and child health, with a long-term goal to reduce community exposures and improve worker health policies, particularly for women and pregnant workers. https://doi.org/10.3390/children11091045

Joint effects of tobacco smoke exposure and heavy metals on serum sex hormones in adult males, Hua, X. G., Hu, R., Chen, C., Sun, J. J., Feng, X. Q. and Zhang, X. J., *Hormones-International Journal of Endocrinology and Metabolism*, 2024 Sep 2024.

ObjectiveThis study aimed to explore the associations of tobacco smoke exposure (TSE) and heavy metal exposure on sex hormones and the joint effects between them in adult males. MethodsThe study used data of 2244 adult males from the National Health and Nutrition Examination Survey (NHANES, 2013-2016). Weighted linear regression models were used to calculate their beta (beta) coefficients and corresponding confidence interval (95% CI), which assessed the joint effects of TSE and heavy metals on sex hormones. ResultsSex hormone-binding globulin (SHBG) showed a positive association with increased per standard deviation (SD) for cotinine (beta=0.024 [0.004, 0.043]; P<0.001), lead (beta=0.021 [0.002, 0.039]; P=0.028), and cadmium (beta=0.034 [0.015, 0.053]; P<0.001). Manganese was positively associated with estradiol (E2) (beta=0.025 [0.009, 0.042]; P=0.002). The subjects with higher cadmium levels were more likely to have higher total testosterone (TT) (beta=0.042 [0.023, 0.062]; P<0.001). TSE and lead exerted synergistic effects on TT (p for interaction = 0.015) and E2 (p for interaction = 0.009), as also did TSE and cadmium on SHBG (p for interaction = 0.037). Compared with the reference group, TSE participants who were exposed to high concentrations of lead, cadmium, mercury, and manganese had significantly elevated TT levels, but these high levels presented no significant association with E2 levels. A significantly higher level of SHBG among TSE participants was detected in high concentrations for lead, cadmium, and mercury. ConclusionTSE exacerbated sex hormone imbalances when combined with high levels of metal exposure. Smoking cessation is crucial, especially in the case of high levels of occupational exposure to heavy metals. https://doi.org/10.1007/s42000-024-00600-8

Perfluoroalkyl and Polyfluoroalkyl Substances in Relation to the Participant-Reported Total Pregnancy and Live Birth Numbers among Reproductive-Aged Women in the United States, Huang, G. T., Li, J. H., Zhou, L. X., Duan, T. T., Deng, L. J., Yang, P. and Gong, Y. J., *Toxics*, Aug 2024, Vol. 12, no. 8.

Perfluoroalkyl and polyfluoroalkyl substances (PFASs), widely utilized in various industries, may pose potential reproductive well-being risks. However, the research on the impact of PFAS exposures on pregnancy and live birth rates remains scarce. To address this gap, we conducted a cross-sectional study using the data from the United States National Health and Nutrition Examination Survey (NHANES) collected between 2013 and 2018. We focused on six PFAS compounds measured in the serum of women aged 20 to 50 years, employing the Poisson regression, Quantile G-composition (Qgcomp), and Weighted Quantile Sum (WQS) regression models. Adjusting for age, racial/ethnic origin, educational level, marital status, family income, body mass

index (BMI), menarche age, birth control pill use, and other female hormone consumption, the Poisson regression identified significant negative associations between the individual PFAS exposures and pregnancy and live birth numbers ($p < 0.05$ for all 24 null hypotheses for which the slope of the trend line is zero). The Qgcomp analysis indicated that a one-quartile increase in the mixed PFAS exposures was associated with reductions of 0.09 (95% CI: -0.15, -0.03) in the pregnancy numbers and 0.12 (95% CI: -0.19, -0.05) in the live birth numbers. Similarly, the WQS analysis revealed that a unit increase in the WQS index corresponded to decreases of 0.14 (95% CI: -0.20, -0.07) in the pregnancy numbers and 0.14 (95% CI: -0.21, -0.06) in the live birth numbers. Among the six specific PFAS compounds we studied, perfluorononanoic acid (PFNA) had the most negative association with the pregnancy and live birth numbers. In conclusion, our findings suggest that PFAS exposures are associated with lower pregnancy and live birth numbers among women of reproductive age. https://doi.org/10.3390/toxics12080613

Prenatal Exposure to Per- and Polyfluoroalkyl Substances and ASD-Related Symptoms in Early Childhood: Mediation Role of Steroids,
Huang, Y., Jia, Z. X., Lu, X. H., Wang, Y., Li, R. Z., Zhou, A. F., Chen, L., Wang, Y. Y., Zeng, H. C., Li, P., Ghassabian, A., Yuan, N. X., Kong, F. J., Xu, S. Q. and Liu, H. X., *Environmental Science & Technology*, Sep 2024, Vol. 58, no. 37, p. 16291-16301.

Previous studies regarding the associations between perfluoroalkyl and polyfluoroalkyl substances (PFAS) and autism spectrum disorder (ASD) have yielded inconsistent results, with the underlying mechanisms remaining unknown. In this study, we quantified 13 PFAS in cord serum samples from 396 neonates and followed the children at age 4 to assess ASD-related symptoms. Our findings revealed associations between certain PFAS and ASD-related symptoms, with a doubling of perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) concentrations associated with respective increases of 1.79, 1.62, and 1.45 units in language-related symptoms and PFDA exhibiting an association with higher score of sensory stimuli. Nonlinear associations were observed in the associations of 6:2 chlorinated polyfluorinated ether sulfonate (Cl-PFAES) and 8:2 Cl-PFAES with ASD-related symptoms. Employing weighted quantile sum (WQS) regression, we observed significant mixture effects of multiple PFAS on all domains of ASD-related symptoms, with PFNA emerging as the most substantial contributor. Assuming causality, we found that 39-40% of the estimated effect of long-chain PFAS (PFUnDA and PFDoDA) exposure on sensory stimuli was mediated by androstenedione. This study provides novel epidemiological data about prenatal PFAS mixture exposure and ASD-related symptoms. https://doi.org/10.1021/acs.est.4c04500

Associations of co-exposure to polycyclic aromatic hydrocarbons and lead (Pb) with IGF1 methylation in peripheral blood of preschool children from an e-waste recycling area,
Huo, X., Xu, X. J., Wang, Q. H., Zhang, J., Hylkema, M. N. and Zeng, Z. J., *Environment International*, Aug 2024, Vol. 190.

Background: Childhood exposure to polycyclic aromatic hydrocarbons (PAHs) or lead (Pb) is associated with epigenetic modifications. However, the effects of their co-exposures on IGF1 (Insulin-like growth factor 1) methylation and the potential role in child physical growth are unclear. Methods: From our previous children study (N = 238, ages of 3-6), 75 children with higher total concentrations of urinary ten hydroxyl PAH metabolites (∑10OH-PAHs) from an e-waste recycling area, Guiyu, and 75 with lower ∑10OH-PAHs from Haojiang (reference area) were included. Pb and IGF1 P2 promoter methylation in peripheral blood were also measured. Multivariable linear regression analyses were performed to estimate individual associations, overall effects and interactions of co-exposure to OH-PAHs and Pb on IGF1 methylation were further explored using Bayesian kernel machine regression. Results: Methylation of IGF1 (CG-232) was lower (38.00 vs. 39.74 %, $P < 0.001$), but of CG-207 and CG-137 were higher (59.94 vs. 58.41 %; 57.60 vs. 56.28 %, both $P < 0.05$) in exposed children than the reference. The elevated urinary 2-OHPhe was associated with reduced methylation of CG-232 ($B = -0.051$, 95 % CI: -0.096, -0.005, $P < 0.05$), whereas blood Pb was positively associated with methylation of CG-108 ($B = 0.106$, 95 %CI: 0.013, 0.199, $P < 0.05$), even after full adjustment. Methylations of CG-224 and 218 significantly decreased when all OH-PAHs and Pb mixtures were set at 35th - 40th and 45th - 55th percentile compared to when all fixed at 50th percentile. There were bivariate interactions of co-exposure to the mixtures on methylations of CG232, 224, 218, and 108. Methylations correlated with height, weight, were observed in the exposed children. Conclusions: Childhood co-exposure to high PAHs and Pb from the e-waste may be associated with IGF1 promoter methylation alterations in peripheral blood. This, in turn, may interrupt the physical growth of preschool children. https://doi.org/10.1016/j.envint.2024.108833

Endocrine-Disrupting Chemicals and the Development of Diabetes Mellitus Type 1: A 5-Year Systematic Review,
Keskesiadou, G. N., Tsokkou, S., Konstantinidis, I., Georgaki, M. N., Sioga, A., Papamitsou, T. and Karachrysafi, S., *International Journal of Molecular Sciences*, Sep 2024, Vol. 25, no. 18.

Introduction: According to the Institute of Environmental Sciences, endocrine-disrupting chemicals (EDCs) are "natural or human-made chemicals that may mimic, block, or interfere with the body's hormones, associated with a wide array of health issues", mainly in the endocrine system. Recent studies have discussed the potential contribution of EDCs as risk factors leading to diabetes mellitus type 1 (T1DM), through various cellular and molecular pathways. Purpose: The purpose of this study was to investigate the correlation between the EDCs and the development of T1DM. Methodology: Thus, a 5-year systematic review was conducted to bring light to this research question. Using the meta-analysis and systematic review guideline protocol, a PRISMA flow diagram was constructed and, using the keywords (diabetes mellitus type 1) AND (endocrine-disrupting chemicals) in the databases PubMed, Scopus and ScienceDirect, the relevant data was collected and extracted into tables. Quality assessment tools were employed to evaluate the quality of the content of each article retrieved. Results: Based on the data collected and extracted from both human and animal studies, an association was found between T1DM and certain EDCs, such as bisphenol A (BPA), bisphenol S (BPS), persistent organic pollutants (POPs), phthalates and dioxins. Moreover, based on the quality assessments performed, using the Newcastle-Ottawa Scale and ARRIVE quality assessment tool, the articles were considered of high quality and thus eligible to justify the correlation of the EDCs and the development of T1DM. Conclusion: Based on the above study, the correlation can be justified; however, additional studies can be made focusing mainly on humans to understand further the pathophysiologic mechanism involved in this association. https://doi.org/10.3390/ijms251810111

Relationship between the use of hair products and urine benzophenone-3: the Korean National Environmental Health Survey (KoNEHS) cycle 4,
Kim, S., Cho, S. Y., Yoon, S., Kim, D., Park, H. W., Huh, S. W. and Kang, J., *Annals of Occupational and Environmental Medicine*, Aug 2024, Vol. 36.

Background: Benzophenone-3 is a type of ketone with 2 benzene rings attached to a carbonyl group (C=O) and one benzene ring attached to a hydroxyl group (-OH). As an endocrinedisrupting chemical, benzophenone-3 is known to be associated with reproductive, developmental, thyroid, and endocrine toxicities. Benzophenone-3 is commonly used in hair products, cosmetics, and ultraviolet (UV) filters because of its characteristic property to absorb UV light. This study aims to investigate the association between the use of hair products and urine benzophenone-3 using the data from the Korean National Environmental Health Survey (KoNEHS) cycle 4 (2018-2020), which represents the Korean population. Methods: Using the KoNEHS cycle 4 survey, the data of 3,796 adults aged >= 19 years were analyzed. Based on the 75th percentile concentration of urine benzophenone-3, the participants were divided into the low- and high-concentration groups. Chi-square test was conducted to analyze the association of urine benzophenone-3 with distribution of general characteristics, use of personal care products, consumption of marine foods, and use of plastic products as the variable. Logistic regression analysis was conducted to calculate odds ratios (ORs) for the high-concentration group of urine benzophenone-3 based on the use of hair products. Results: Women with < 6 times or >= 6 times of hair product usage had significantly higher adjusted ORs compared to those who did not use hair products. The calculated ORs were 1.24 (95% confidence interval [CI]: 1.12-1.38) for women with < 6 times of usage and 1.54 (95% CI: 1.33-1.79) for women with >= 6 times of usage. Conclusions: This study revealed the association between the use of hair products and the concentration of urine benzophenone-3 in the general Korean population. https://doi.org/10.35371/aoem.2024.36.e20

The effect of endocrine-disrupting chemicals in follicular fluid: The insights from oocyte to fertilization, Li, J. H., Zhou, L. X., Huang, S. Y., Duan, T. T., Xie, J. Y., Li, X. J., Deng, L. J., Zeng, C. Y., Jing, F. R., Zhu, S., Liu, C. Q., Gong, Y. J., Shu, Y. Q., Shen, X. T. and Yang, P., *Environment International*, Sep 2024, Vol. 191.

Endocrine-disrupting chemicals (EDCs) exhibited the detriment in female reproductive health. Our objective was to investigate the individual and mixture effects of EDCs present in follicular fluid, the environment in which oocytes grow and develop, on early reproductive outcomes. We recruited 188 women seeking reproduction examination from the Study of Exposure and Reproductive Health (SEARCH) cohort between December 2020 and November 2021. We assessed the concentrations of 7 categories of 64 EDCs in follicular fluid, and measured early reproductive outcomes, including retrieved oocytes, mature oocytes, normal fertilized oocytes,

and highquality embryos. In this study Monomethyl phthalate (MMP) (2.17 ng/ml) were the compounds found in the highest median concentrations in follicular fluid. After adjusting for multiple testing, multivariate regression showed that multiple EDCs were significantly negatively associated with early assisted reproduction outcomes. For example, MMP showed a significant negative correlation with the number of high quality embryos (beta: -0.1, 95% CI: -0.15, -0.04). Specifically, eight types of EDCs were significantly negatively associated with four early assisted reproductive outcomes (beta range: -0.2 similar to -0.03). In the mixed exposure model, we found that mixtures of EDC were significantly negatively correlated with all four outcomes. In the quantile g-computation (QGCOMP) model, for each interquartile range increase in the concentration of EDC mixtures, the number of oocytes retrieved, mature oocytes, normally fertilized oocytes, and high-quality embryos decreased by 0.46, 0.52, 0.77, and 1.2, respectively. Moreover, we identified that phthalates (PAEs) predominantly contributed to the negative effects. Future research should validate our findings. https://doi.org/10.1016/j.envint.2024.108957

Association of blood isobutyronitrile with infertility among reproductive-aged women: Results from the NHANES cohort,
Li, P. Y. and Chen, Z. Y., *Ecotoxicology and Environmental Safety*, Oct 2024, Vol. 284.

Isobutyronitrile finds extensive application in organic synthesis for the production of the insecticide diazinon. Apart from occupational exposure, cigarette smoking may also expose the general population to isobutyronitrile. However, to date, the association between isobutyronitrile and female infertility has not been explored in a population-based study. Hence, we analysed data from 1254 women, aged 18-44, with blood isobutyronitrile results and infertility questionnaires, from National Health and Nutrition Examination Survey (NHANES) 2015-2016 and NHANES 2017-March 2020. To compare differences, weighted chi-square tests were conducted for categorical variables and weighted regression models were performed for continuous variables. Logistic regression and generalized linear models were applied to examine the associations. Each standard deviation increment (SD=0.026) of isobutyronitrile increased the risk of infertility by 24 % after adjusting for potential confounders in logistic regression model (aOR=1.24; 95 % CI: 1.06-1.46). In women who had been pregnant and gave birth, the results exhibited a consistent linear relationship. The participants were classified into two groups, namely positive and negative, using an isobutyronitrile cut-off value that exceeded 0.040 ng/mL. The positive group did not demonstrate a statistically significant correlation (aOR=1.55; 95 % CI: 0.66-3.65). According to smooth curve fitting, isobutyronitrile and infertility was linearly related across the entire range, and no threshold effect was found. Particularly, non-Hispanic Black women had a significantly stronger association with isobutyronitrile exposure and infertility (aOR=4.27; 95 % CI: 1.32-13.83). In conclusion, our study was the first report of an independent association of isobutyronitrile with infertility, especially in non-Hispanic Black women. Additional fundamental research on nonhuman primates, along with comprehensive clinical studies, are necessary to fully elucidate the intricate mechanisms underlying isobutyronitrile activity. https://doi.org/10.1016/j.ecoenv.2024.117010

Prenatal co-exposure to phthalate metabolites and bisphenols among non-syndromic cleft lip and/or palate in offspring,
Li, S. N., Zhu, H. Y., Yang, C., Wang, C. R., Liu, J. F., Jin, L., Li, Z. W., Ren, A. G. and Wang, L. L., *Environmental Pollution*, Dec 2024, Vol. 362.

Phthalate metabolites and bisphenols can cause adverse pregnancy outcomes. However, there is no study to evaluate the associations of prenatal exposure to phthalate metabolites and bisphenols with non-syndromic cleft lip and/or palate (NSCL/P) risk in offspring. A population-based case-control study was conducted in a multicenter setting from 2005 to 2021, enrolling 448 pregnant women. Seven phthalate metabolites and six bisphenols were quantified in placenta using liquid chromatography-tandem mass spectrometry. In the logistic regression analysis, high levels of mono-ethyl phthalate, mono-cyclohexyl phthalate, mono-octyl phthalate, bisphenol A, bisphenol AF, bisphenol AP, and fluorene-9-bisphenol were associated with increased NSCL/P risk with odds ratios (95% confidence intervals) of 1.86(1.07,3.25), 6.56(3.47,12.39), 8.49(4.44,16.24), 8.34(4.32,16.08), 3.19 (1.81,5.62), 2.78(1.59,4.86), and 5.16(2.82,9.44). The Bayesian kernel machine regression model revealed that co-exposure to phthalate metabolites and bisphenols was associated with increased NSCL/P risk. Similarly, quantile-based g-computation analysis indicated that each quantile increase in mixture concentration was positively related to higher risk for NSCL/P [odds ratio (95% confidence interval) = 2.98(1.97,4.51)]. This study provides novel evidence that prenatal single and co-exposure to phthalate metabolites and bisphenols were associated with increased NSCL/P risk, suggesting that exposure to phthalate metabolites and bisphenols during pregnancy should be minimized to reduce the incidence of NSCL/P in offspring. https://doi.org/10.1016/j.envpol.2024.125001

Association between serum levels of 4-tertiary-octylphenol and thyroid function in a young cohort study,
Lin, C. Y., Lee, H. L., Chen, C. W., Sung, F. C. and Su, T. C., *Journal of Hazardous Materials Advances*, Nov 2024, Vol. 16.

4-tertiary-octylphenol (4-t-OP) is a commonly used alkylphenol present in a variety of consumer products. Earlier experimental investigations have suggested that 4-t-OP leads to thyroid dysfunction. However, it is unclear whether these effects translate to humans. We recruited 886 adolescents and young adults (aged 12-30 years) from Taiwan and explored the associations between serum levels of 4-t-OP and various thyroid panel parameters including free and total thyroxine (T4) and triiodothyronine (T3), thyroid-stimulating hormone (TSH), and thyroxine-binding globulin (TBG). Our findings indicated that a one-unit increase in the natural logarithm (ln) of 4-t-OP levels was positively associated with both total T3 and ln free T4, with beta values of 3.122 (SE = 1.400, P = 0.026) and 0.046 (SE = 0.015, P = 0.002), respectively. Furthermore, we observed a statistically significant upward trend in the mean values of total T3 and ln free T4 as the quartiles of 4-t-OP exposure increased (P for trend = 0.001 and 0.025, respectively). Nevertheless, our analysis did not uncover any differences in the odds ratio of thyroid diseases based on exposure to 4-t-OP in the logistic regression analysis. In conclusion, our study reveals an association between serum concentrations of 4-t-OP and biomarkers of thyroid function. However, these effects may manifest as subclinical. Further investigations are essential to establish a causal relationship between 4-t-OP exposure and thyroid function in human subjects. https://doi.org/10.1016/j.hazadv.2024.100476

Prenatal EDC exposure, DNA Methylation, and early childhood growth: A prospective birth cohort study,
Lv, Y. Q., Jia, Z. X., Wang, Y., Huang, Y. Z., Li, C. X., Chen, X. M., Xia, W., Liu, H. X., Xu, S. Q. and Li, Y. Y., *Environment International*, Aug 2024, Vol. 190.

Background: Exposure to endocrine-disrupting chemicals (EDCs) has been found to be associated with growth and developmental abnormalities in children. However, the potential mechanisms by which exposure to EDCs during pregnancy increases the risk of obesity in children remain unclear. Objective: We aimed to explore associations between prenatal EDC exposure and the body mass index (BMI) of children at age two, and to further explore the potential impact of DNA methylation (DNAm). Method: This study included 285 mother-child pairs from a birth cohort conducted in Wuhan, China. The BMI of each child was assessed at around 24 months of age. The concentrations of sixteen EDCs at the 1st, 2nd, and 3rd trimesters were measured using ultra-high performance liquid chromatography coupled to a triple quadrupole mass spectrometer. The research utilized general linear models, weighted quantile sum regression, and Bayesian Kernel Machine Regression to assess the association between prenatal EDC exposure and childhood BMI z-scores (BMIz). Cord blood DNAm was measured using the Human Methylation EPIC BeadChip array. An epigenomewide DNAm association study related to BMIz was performed using robust linear models. Mediation analysis was then applied to explore potential mediators of DNAm. Results: Urinary concentrations of seven EDCs were positively associated with BMIz in the 1st trimester, which remained significant in the WQS model. A total of 641 differential DNAm positions were associated with elevated BMIz. Twelve CpG positions (annotated to DUXA, TMEM132C, SEC13, ID4, GRM4, C2CD2, PRAC1&PRAC2, TSPAN6 and DNAH10) mediated the associations between urine BP-3/BPS/MEP/TCS and elevated BMIz (P < 0.05). Conclusion: Our results revealed that prenatal exposure to EDCs was associated with a higher risk of childhood obesity, with specific DNAm acting as a partial mediator. https://doi.org/10.1016/j.envint.2024.108872

Carcinogenic industrial air pollution and postmenopausal breast cancer risk in the National Institutes of Health AARP Diet and Health Study,
Madrigal, J. M., Pruitt, C. N., Fisher, J. A., Liao, L. M., Graubard, B. I., Gierach, G. L., Silverman, D. T., Ward, M. H. and Jones, R. R., *Environment International*, Sep 2024, Vol. 191.

Background: Chemicals emitted from industrial facilities include known or suspected mammary carcinogens and endocrine disruptors, but epidemiologic studies are limited. We evaluated associations between air emissions of multiple carcinogenic chemicals and postmenopausal breast cancer risk in a large prospective U.S. cohort. Methods: We used the U.S. Environmental Protection Agency's Toxics Release Inventory to estimate historical airborne emissions (1987-1995) of 19 known and probable carcinogens for participants enrolled (1995-1996) in the NIH-AARP Diet and Health Study. Among 170,402 women, 15,124 breast cancers were diagnosed through 2018. We constructed inverse distance- and wind-weighted average emissions

metrics within 1, 2, 5, and 10 km of the enrollment address for each chemical. We estimated multivariable adjusted HRs and 95 % CIs for categories (quartiles, tertiles, medians) of each chemical in association with breast cancer overall and separately by type (invasive, ductal carcinoma in situ) and estrogen receptor (ER) status. Results: We observed an association between benzene emissions and breast cancer risk that was strongest at 1 km (HRQ4 vs. non-exposed = 2.06, 95 %CI: 1.34-3.17; p-trend = 0.001). The magnitude of the association weakened with increasing distance (2 km HRQ4 vs. non-exposed = 1.17, 95 %CI=0.92-1.49; p-trend = 0.19; 5 km HRQ4 vs. non-exposed = 1.05, 95 %CI=0.94-1.16; p-trend = 0.37; 10 km HRQ4 vs. non-exposed = 0.95, 95 % CI=0.89-1.02; p-trend = 0.19) and appeared to be most relevant for invasive rather than intraductal disease. Overall risk was also elevated for vinyl chloride at 5 km (HR >= median vs. non-exposed = 1.20, 95 %CI=1.01-1.43; p-trend = 0.04), but not 2 km or 10 km. We observed suggestive associations for asbestos, trichloroethylene, and styrene in different subgroup analyses, but risk patterns were not clear across distances. Associations with other chemicals were generally null, with limited evidence of heterogeneity by disease type or ER status. Conclusions: An increased risk of breast cancer associated with relatively high levels of industrial benzene emissions warrants additional study, particularly among participants with diverse sociodemographic characteristics that live in areas with higher density of industrial facilities. https://doi.org/10.1016/j.envint.2024.108985

Exploring the association between urinary bisphenol A, S, and F levels and semen quality parameters: Findings from Led-Fertyl cross-sectional study,
Martínez, M. A., Salas-Huetos, A., De La Puente, M. F., Valle-Hita, C., Marquès, M., Del Egido-González, C., Davila-Cordova, E., Mestres, C., Petersen, M. S., Babio, N. and Salas-Salvadó, J., *Environmental Research*, Dec 2024, Vol. 263.

Infertility is recognized as a multifaceted condition affecting approximately 15% of couples globally, influenced by various factors including genetic predisposition and environmental exposures. Among these environmental factors, bisphenol A (BPA) emerges as a prominent Endocrine-disrupting chemical (EDCs) widely distributed, leading to chronic human exposure in daily life. As regulations on BPA became more stringent, alternative substances such as bisphenol S (BPS) and bisphenol F (BPF) have emerged. Animal studies have demonstrated a dose-dependent decline in fertility and embryotoxicity following chronic exposure to BPA. However, literature data on human studies are limited and heterogeneous. Additionally, even less is known about the relationship between exposure to the BPA analogues (BPS and BPF) and sperm quality. Therefore, the present study aimed to examine the association between urinary concentrations of BPA, BPF, and BPS and semen quality parameters among 195 adult Spanish men from the Led-Fertyl study cohort using multiple linear regression models adjusted by potential confounding variables. Our results revealed an inverse association between log-transformed creatinine-adjusted concentration (ng/mg) of BPA and BPF levels and the percentage of sperm vitality (/i: 3.56 %; 95%CI: 6.48 to -0.63 and /i: 4.14 %; 95%CI: 6.97 to -1.31; respectively). Furthermore, participants in the highest quartile of BPA and BPF urinary concentration exhibited lower sperm vitality compared to those in the lowest quartile (/i: 6.90 %; 95%CI: 11.60 to -2.15 and /i: 9.68 %; 95%CI: 14.43 to -4.94; respectively). These results supply epidemiological evidence establishing a relationship between bisphenols urine exposure and sperm quality, suggesting that a re-evaluation of the overall safety of BPA alternatives is warranted. https://doi.org/10.1016/j.envres.2024.120086

Associations of urinary biomarkers of phthalates, phenols, parabens, and organophosphate esters with glycemic traits in pregnancy: The Healthy Start Study,
Peng, M. Q., Dabelea, D., Adgate, J. L., Perng, W., Calafat, A. M., Kannan, K. and Starling, A. P., *Environmental Research*, Dec 2024, Vol. 262.

Background: Certain endocrine-disrupting chemicals (EDCs) are widespread in consumer products and may alter glucose metabolism. However, the impact of EDC exposures on glucose and insulin regulation during pregnancy is incompletely understood, despite potential adverse consequences for maternal and infant health. We estimated associations between 37 urinary biomarkers of EDCs and glucose-insulin traits among pregnant women. Methods: Seventeen phthalate or phthalate substitute metabolites, six environmental phenols, four parabens, and ten organophosphate ester metabolites were quantified in mid-pregnancy urine from 298 participants in the Healthy Start Study. Fasting blood glucose, insulin, and hemoglobin A1c were assessed concurrently, and Homeostasis Model Assessment 2-Insulin Resistance (HOMA2-IR) was calculated. Gestational diabetes diagnoses and screening results were obtained from medical records for a subset of participants. We estimated associations between each EDC and outcome separately using linear and robust Poisson regression models and analyzed EDC mixture effects. Results: The EDC mixture was positively associated with glucose, insulin, and HOMA2-IR, although overall associations were attenuated after

adjustment for maternal BMI. Two mixture approaches identified di(2ethylhexyl) phthalate (DEHP) metabolites as top contributors to the mixture's positive associations. In singlepollutant models, DEHP metabolites were positively associated with fasting glucose, fasting insulin, and HOMA2-IR even after adjustment for maternal BMI. For example, each interquartile range increase in log2transformed mono(2-ethyl-5-oxohexyl) phthalate was associated with 2.4 mg/dL (95% confidence interval (CI): 1.1, 3.6) higher fasting glucose, 11.8% (95%CI: 3.6, 20.5) higher fasting insulin, and 12.3% (95%CI: 4.2, 21.1) higher HOMA2-IR. Few EDCs were associated with hemoglobin A1c or with a combined outcome of impaired glucose tolerance or gestational diabetes. Discussion: Exposures to phthalates and particularly DEHP during pregnancy are associated with altered glucoseinsulin regulation. Disruptions in maternal glucose metabolism during pregnancy may contribute to adverse pregnancy outcomes including gestational diabetes and fetal macrosomia, and associated long-term consequences for maternal and child health. https://doi.org/10.1016/j.envres.2024.119810

Impact of Bisphenol A and its alternatives on oocyte health: a scoping review,
Peters, A. E., Ford, E. A., Roman, S. D., Bromfield, E. G., Nixon, B., Pringle, K. G. and Sutherland, J. M., *Human Reproduction Update*, Sep 2024, Vol. 30, no. 6, p. 653-691.

BACKGROUND Bisphenol A (BPA) is an endocrine disrupting chemical released from plastic materials, including food packaging and dental sealants, persisting in the environment and ubiquitously contaminating ecosystems and human populations. BPA can elicit an array of damaging health effects and, alarmingly, 'BPA-free' alternatives mirror these harmful effects. Bisphenol exposure can negatively impact female fertility, damaging both the ovary and oocytes therein. Such damage can diminish reproductive capacity, pregnancy success, and offspring health. Despite global government regulations in place to indicate 'safe' BPA exposure levels, these policies have not considered the effects of bisphenols on oocyte health. OBJECTIVE AND RATIONALE This scoping review was conducted to evaluate evidence on the effects of BPA and BPA alternatives on standardized parameters of oocyte health. In doing so, this review addresses a critical gap in the literature providing a comprehensive, up-to-date synthesis of the effects of bisphenols on oocyte health. SEARCH METHODS This scoping review was conducted in accordance with PRISMA guidelines. Four databases, Medline, Embase, Scopus, and Web of Science, were searched twice (23 February 2022 and 1 August 2023) to capture studies assessing mammalian oocyte health post-bisphenol exposure. Search terms regarding oocytes, ovarian follicles, and bisphenols were utilized to identify relevant studies. Manuscripts written in English and reporting the effect of any bisphenol on mammalian oocyte health from all years were included. Parameters for toxicological studies were evaluated, including the number of bisphenol concentrations/doses tested, dosing regimen, biological replicates and/or animal numbers, and statistical information (for human studies). Standardized parameters of oocyte health including follicle counts, oocyte yield, oocyte meiotic capacity, morphology of oocyte and cumulus cells, and oocyte meiotic spindle integrity were extracted across the studies. OUTCOMES After screening 3147 studies, 107 studies of either humans or mammalian animal models or humans were included. Of the in vitro exposure studies, 96.3% (26/27) and 94.1% (16/17) found at least one adverse effect on oocyte health using BPA or BPA alternatives (including BHPF, BPAF, BPB, BPF, and BPS), respectively. These included increased meiotic cell cycle arrest, altered morphology, and abnormal meiotic spindle/chromosomal alignment. In vivo, 85.7% (30/35) of studies on BPA and 92.3% (12/13) on BPA alternatives documented adverse effects on follicle development, morphology, or spindle/chromosome alignment. Importantly, these effects were recorded using levels below those deemed 'safe' for human exposure. Over half (11/21) of all human observational studies showed associations between higher urinary BPA levels and reduced antral follicle counts or oocyte yield in IVF patients. Recommendations are presented based on the identified shortcomings of the current evidence, incorporating elements of FDA requirements for future research in the field. WIDER IMPLICATIONS These data highlight the detrimental impacts of low-level BPA and BPA alternative exposure, contributing to poor oocyte quality and reduced fertility. These outcomes are valuable in promoting the revision of current policies and guidelines pertaining to BPA exposure internationally. This study serves as a valuable resource to scientists, providing key recommendations on study design, reporting elements, and endpoint measures to strengthen future studies. Ultimately, this review highlights oocyte health as a fundamentally important endpoint in reproductive toxicological studies, indicating an important direction for future research into endocrine disrupting chemicals to improve fertility outcomes. Graphical Abstract Exposure to BPA and BPA alternatives, at doses considered safe, has detrimental impacts on key oocyte health outcomes, impacting fertility success across generations. https://doi.org/10.1093/humupd/dmae025

Chemical exposome and children health: Identification of dose-response relationships from meta-analyses and epidemiological studies,

Rocabois, A., Sanchez, M., Philippat, C., Crépet, A., Vrijheid, M., Nieuwenhuijsen, M. and Slama, R., *Environmental Research*, Dec 2024, Vol. 262.

Background: Health impact assessment studies quantifying the impact of the chemical exposome on children's health generally consider a small fraction of the exposome. Synthetizing available dose-response relationships is an essential step to fill this gap. We reviewed the literature for dose-response relationships relating the chemical exposome with children health. Method: We focused on 78 substance-outcome pairs for which the level of evidence had previously been classified as 'likely' or 'very likely'. We searched for dose-response relationships for these pairs from meta-analyses and, if none was available, from single epidemiological studies, from which we conducted meta-analyses whenever possible. Results: We identified dose-response relationships for 50 of the 78 prioritized substance-outcome pairs (64%). Dose-response relationships stemmed from meta-analyses for 21 pairs, from de novo meta-analyses for 1 pair and single studies for 28 pairs. Dose-response relationships were available for tobacco (fetal and infant death, congenital heart defects, birth outcomes, orofacial clefts, respiratory health), lead (asthma, cognition, delayed puberty onset and iron deficiency anaemia), polychlorobiphenyls (PCBs) (cognition, respiratory infections and birth outcomes), bisphenol A (cognition), hexachlorobenzene (HCB) (respiratory health), Polybrominated diphenyl ethers (neurodevelopment), DDT (hypospadias, cryptorchidism, miscarriage), pesticides (neurodevelopment), methylmercury (cognition), PFAS (immune system, birth weight, behavior, miscarriage), arsenic (cognition, birth weight, death, respiratory health), cadmium (cognition, birth weight), manganese (behavior), sodium (blood pressure) and thallium (birth weight). For 28 of the 78 substance-outcome pairs (36%), no doseresponse relationship was available from epidemiological studies in children. Conclusions: We identified dose-response relationships for 50 substance-outcome pairs, corresponding to 20 chemicals and 17 health outcomes. These can be used to perform more comprehensive quantitative health impact assessment of the exposome on child health. We also identified 28 substance-outcome pairs corresponding to 'likely' or 'very likely' effects for which research generating dose-response functions in children would be relevant. https://doi.org/10.1016/j.envres.2024.119811

Prenatal exposure to PFAS and the association with neurobehavioral and social development during childhood,
Saha, T., Gbemavo, M. C. J., Booij, L., Arbuckle, T. E., Ashley-Martin, J., Fisher, M., Muckle, G., Lanphear, B., Asztalos, E., Seguin, J. and Bouchard, M. F., *International Journal of Hygiene and Environmental Health*, Jan 2025, Vol. 263.

Exposure to per- and polyfluoroalkyl substances (PFAS) is ubiquitous and may be associated with neurodevelopmental toxicity. However, epidemiological studies report mixed results on the risks of gestational PFAS exposure for children's neurobehavioral impairment. We aimed to examine the associations between prenatal PFAS exposure and children's neurobehavioral and social problems. We measured plasma concentrations of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulphonate (PFHxS) in first-trimester blood from 757 women from the Canadian MaternalInfant Research on Environmental Chemicals (MIREC) study. Children were assessed at 3-4 years with the Behavior Assessment System for Children-2 (BASC-2) and the Social Responsiveness Scale-2 (SRS-2) (n = 756 and 496, respectively). We used multivariable linear regression to examine associations between individual and summed log2-transformed PFAS and scores on these assessments. Effect modification by sex was evaluated through interaction terms and stratified analyses. In the sample combining both sexes, a doubling of maternal PFOA was significantly associated with lower Tscores on the following SRS-2 scales: Social Motivation, DSM-Social Communication, and SRS Total score (B ranging from -1.08 to -0.78), suggesting lesser impairments with higher exposure. In sex-stratified analysis, PFOA was related to significantly lower T-scores in boys for these BASC-2 scales: Behavioral Symptoms Index, Externalizing Problems, Aggression, and Hyperactivity (B ranging from -1.32 to -1.03). In girls, however, PFAS were significantly associated more problem behaviors, but most associations were small and the CIs included the null, with the exception of PFOA being significantly associated with higher T-scores for the BASC-2Anxiety scale (B = 1.84, 95% CI: 0.36, 3.32). In conclusion, we did not observe strong associations between prenatal exposure to the PFAS evaluated and children's neurobehavioral and social development in this population with low exposure levels. The results show mixed findings, depending on children's sex, neurodevelopmental outcome, and specific PFAS. https://doi.org/10.1016/j.ijheh.2024.114469

Associations between Urinary Phthalate Metabolites with BDNF and Behavioral Function among European Children from Five HBM4EU Aligned Studies,

Salamanca-Fernández, E., Espín-Moreno, L., Olivas-Martínez, A., Pérez-Cantero, A., Martín-Rodríguez, J. L., Poyatos, R. M., Barbone, F., Rosolen, V., Mariuz, M., Ronfani, L., Murínová, L. P., Fábelová, L., Szigeti, T., Kakucs, R., Sakhi, A. K., Haug, L. S., Lindeman, B., Tratnik, J. S., Kosjek, T., Jacobs, G., Voorspoels, S., Jurdakova, H., Gorova, R., Petrovicová, I., Kolena, B., Esteban, M., Pedraza-Díaz, S., Kolossa-Gehring, M., Remy, S., Govarts, E., Schoeters, G., Fernández, M. F. and Mustieles, V., *Toxics*, Sep 2024, Vol. 12, no. 9.

Based on toxicological evidence, children's exposure to phthalates may contribute to altered neurodevelopment and abnormal regulation of brain-derived neurotrophic factor (BDNF). We analyzed data from five aligned studies of the Human Biomonitoring for Europe (HBM4EU) project. Ten phthalate metabolites and protein BDNF levels were measured in the urine samples of 1148 children aged 6-12 years from Italy (NACII-IT cohort), Slovakia (PCB-SK cohort), Hungary (InAirQ-HU cohort) and Norway (NEBII-NO). Serum BDNF was also available in 124 Slovenian children (CRP-SLO cohort). Children's total, externalizing and internalizing behavioral problems were assessed using the Child Behavior Checklist at 7 years of age (only available in the NACII-IT cohort). Adjusted linear and negative binomial regression models were fitted, together with weighted quantile sum (WQS) regression models to assess phthalate mixture associations. Results showed that, in boys but not girls of the NACII-IT cohort, each natural-log-unit increase in mono-n-butyl phthalate (MnBP) and Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) was cross-sectionally associated with higher externalizing problems [incidence rate ratio (IRR): 1.20; 95% CI: 1.02, 1.42 and 1.26; 95% CI: 1.03, 1.55, respectively]. A suggestive mixture association with externalizing problems was also observed per each tertile mixture increase in the whole population (WQS-IRR = 1.15; 95% CI: 0.97, 1.36) and boys (IRR = 1.20; 95% CI: 0.96, 1.49). In NACII-IT, PCB-SK, InAirQ-HU and NEBII-NO cohorts together, urinary phthalate metabolites were strongly associated with higher urinary BDNF levels, with WQS regression confirming a mixture association in the whole population (percent change (PC) = 25.9%; 95% CI: 17.6, 34.7), in girls (PC = 18.6%; 95% CI: 7.92, 30.5) and mainly among boys (PC = 36.0%; 95% CI: 24.3, 48.9). Among CRP-SLO boys, each natural-log-unit increase in & sum;DINCH concentration was associated with lower serum BDNF levels (PC: -8.8%; 95% CI: -16.7, -0.3). In the NACII-IT cohort, each natural-log-unit increase in urinary BDNF levels predicted worse internalizing scores among all children (IRR: 1.15; 95% CI: 1.00, 1.32). Results suggest that (1) children's exposure to di-n-butyl phthalate (DnBP) and di(2-ethylhexyl) phthalate (DEHP) metabolites is associated with more externalizing problems in boys, (2) higher exposure to DINCH may associate with lower systemic BDNF levels in boys, (3) higher phthalate exposure is associated with higher urinary BDNF concentrations (although caution is needed since the possibility of a "urine concentration bias" that could also explain these associations in noncausal terms was identified) and (4) higher urinary BDNF concentrations may predict internalizing problems. Given this is the first study to examine the relationship between phthalate metabolite exposure and BDNF biomarkers, future studies are needed to validate the observed associations. https://doi.org/10.3390/toxics12090642

Cadmium Associated Preeclampsia: A Systematic Literature Review of Pregnancy and Birth Outcomes,
Sardar, F., Kamsani, Y. S., Ramly, F., Khan, N., Sardar, R. and Aminuddin, A. A., *Biological Trace Element Research*, 2024 Sep 2024.

Preeclampsia (PE), caused by multiple factors, is one of the most serious complications of pregnancy. Cadmium (Cd) is a heavy metal environmental pollutant, reproductive toxicant, and endocrine disruptor, which can increase the risk of PE. Cd toxicity due to occupational, diet, and environmental factors has worsened the risk. Studies showed elevated Cd concentration in maternal blood and placenta of PE women. However, the implicit association between Cd associated PE is still not highlighted. We systematically reviewed Cd-associated PE and its effect on pregnancy and birth outcomes. Based on "Preferred reporting items for systematic reviews and meta-analyses (PRISMA)" guidelines, eighty-six studies were identified by PubMed, Web of Science (WOS), and Scopus databases. Publications were included until October 2023 and articles screened based on our inclusion criteria. Our study identified that the exposure of controlled and uncontrolled Cd induces PE, which negatively affects pregnancy and birth outcomes. Given the serious nature of this finding, Cd is a potential adverse agent that impacts pregnancy and future neonatal health. Further comprehensive studies covering the whole trimesters of pregnancy and neonatal developments are warranted. Data on the molecular mechanisms behind Cd-induced PE is also essential for potential preventive, diagnostic, or therapeutic targets. https://doi.org/10.1007/s12011-024-04364-5

A prospective cohort study of persistent endocrine-disrupting chemicals and perceived stress,

Schildroth, S., Wesselink, A. K., Bethea, T. N., Henn, B. C., Friedman, A., Fruh, V., Coleman, C. M., Lovett, S. M., Vines, A., Sjodin, A., Botelho, J. C., Calafat, A. M., Wegienka, G., Weuve, J., Baird, D. D. and Wise, L. A., *American Journal of Epidemiology*, 2024 Oct 2024.

Persistent endocrine-disrupting chemicals (EDCs) can dysregulate the stress response. We evaluated associations between persistent EDCs and perceived stress among participants in the Study of Environment, Lifestyle, and Fibroids (n = 1394), a prospective cohort study of Black women. Participants completed the Perceived Stress Scale 4 (PSS-4) at baseline and every 20 months through 60 months (score range: 0-16); higher scores indicate higher stress. Endocrine-disrupting chemicals, including per- and polyfluoroalkyl substances, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and organochlorine pesticides, were quantified in plasma samples at baseline. We fit bayesian kernel machine regression and linear mixed-effects models to estimate associations of EDCs (as a mixture and individually) with PSS-4 scores at baseline and at each follow-up visit, respectively. Increasing percentiles of the mixture were not strongly associated with PSS-4 scores at baseline, and no interactions were observed among EDCs. Several individual EDCs (eg, perfluorodecanoic acid, PCB 118, PBDE 99) were associated with higher PSS-4 scores at baseline or follow-up, and other EDCs (eg PCB 138/158) were associated with lower PSS-4 scores at baseline or follow-up. The directionality of associations for individual EDCs was inconsistent across follow-up visits. In conclusion, specific EDCs may be associated with perceived stress in Black women. https://doi.org/10.1093/aje/kwae088

Urinary benzophenone-3 concentrations and ovarian reserve in a cohort of subfertile women,
Silva, E. L., Minguez-Alarcón, L., Coull, B., Hart, J. E., James-Todd, T., Calafat, A. M., Ford, J. B., Hauser, R. and Mahalingaiah, S., *Fertility and Sterility*, Sep 2024, Vol. 122, no. 3, p. 494-503.

Objective: To evaluate the association between the urinary benzophenone-3 concentrations and measures of ovarian reserve (OR) among women in the Environment and Reproductive Health study seeking fertility treatment at Massachusetts General Hospital (MGH) in Boston, Massachusetts. Design: Prospective cohort study. Setting: MGH infertility clinic in Boston, Massachusetts. Patient(s): Women in the Environment and Reproductive Health cohort seeking fertility treatment. Intervention(s): Women contributed spot urine samples prior to assessment of OR outcomes that were analyzed for benzophenone-3 concentrations. Main outcome measure(s): Antral follicle count (AFC) and day 3 follicle-stimulating hormone (FSH) levels were evaluated as part of standard infertility workups during unstimulated menstrual cycles. Quasi-Poisson and linear regression models were used to evaluate the association of the specific gravity-adjusted urinary benzophenone-3 concentrations with AFC and FSH, with adjustment for age and physical activity. In the secondary analyses, models were stratified by age. Result(s): This study included 142 women (mean age +/- standard deviation, 36.1 +/- 4.6 years; range, 22-45 years) enrolled between 2009 and 2017 with both urinary benzophenone-3 and AFC measurements and 57 women with benzophenone-3 and FSH measurements. Most women were White (78%) and highly educated (49% with a graduate degree). Women contributed a mean of 2.7 urine samples (range, 1-10), with 37% contributing >= 2 samples. Benzophenone-3 was detected in 98% of samples. The geometric mean specific gravity-corrected urinary benzophenone-3 concentration was 85.9 mu g/L (geometric standard deviation, 6.2). There were no associations of benzophenone-3 with AFC and day 3 FSH in the full cohort. In stratified models, a 1-unit increase in the log geometric mean benzophenone-3 concentration was associated with a 0.91 (95% confidence interval, 0.86-0.97) times lower AFC among women aged <= 35 years and an increase in the FSH concentration of 0.73 (95% confidence interval, 0.12-1.34) IU/L among women aged >35 years. Conclusion(s): In the main models, urinary benzophenone-3 was not associated with OR. However, younger patients may be vulnerable to the potential effects of benzophenone-3 on AFC. Further research is warranted. https://doi.org/10.1016/j.fertnstert.2024.04.032

A Prospective Analysis of Per- and Polyfluoroalkyl Substances from Early Pregnancy to Delivery in the Atlanta African American Maternal–Child Cohort,
Tan, Y., Eick, S. M., Dunlop, A. L., Barr, D. B., Taibl, K. R., Steenland, K., Kannan, K., Robinson, M., Chang, C.-J., Panuwet, P., Yakimavets, V., Marsit, C. J., Ryan, P. B. and Liang, D., *Environmental Health Perspectives*, 2024, Vol. 132, no. 11, p. 117001.

https://doi.org/10.1289/EHP14334

Per- and polyfluoroalkyl substances (PFAS) exposure and thyroid cancer: Systematic review and meta-analysis,

Van Gerwen, M., Chung, T., Monaghan, M., Vermeulen, R., Petrick, L. and Leung, A. M., *Toxicology Letters*, Aug 2024, Vol. 399, p. 52-58.

Per- and polyfluoroalkyl substances (PFAS) exposure is a potential risk factor for thyroid cancer and may be a contributor to the increasing thyroid cancer incidence rates. A systematic review and meta-analysis was performed to summarize all human studies to date investigating the association between PFAS exposure and thyroid cancer. A search of the National Library of Medicine and National Institutes of Health PubMed and Scopus databases was done to identify relevant articles published in English through January 2024. Studies reporting the association between PFAS exposure and thyroid cancer using odds ratios (OR) were included in the meta-analysis with summary estimate calculated using a random effects model (n=5). Perfluorooctanoic acid (PFOA) was the most investigated PFAS. Results of the included studies varied, ranging from significant positive to significant negative associations with thyroid cancer incidence for different PFAS. Meta-analyses of PFOA, Perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS) were not significant. This comprehensive review of the current literature highlights the limited knowledge and inconsistent results of this association. Large longitudinal cohort studies with varying time between sample collection and thyroid cancer diagnosis are needed to better understand the role of PFAS exposure on thyroid carcinogenesis. https://doi.org/10.1016/j.toxlet.2024.07.910

Exposure to ambient polycyclic aromatic hydrocarbons and early-onset female breast cancer in a case-control study in Ontario, Canada,
Waddingham, C. M., Hinton, P., Villeneuve, P. J., Brook, J. R., Lavigne, E., Larsen, K., King, W. D., Wen, D. Y., Meng, J., Zhang, J. H., Galarneau, E. and Harris, S. A., *Environmental Epidemiology*, Oct 2024, Vol. 8, no. 5.

Background: Ambient polycyclic aromatic hydrocarbons (PAHs) are a class of toxicologically important and understudied air pollutants. Epidemiologic evidence suggests that chronic exposure to PAHs increases breast cancer risk; however, there are few studies in nonoccupational settings that focus on early-onset diagnoses. Methods: The relationship between residentially-based ambient PAH concentrations and female breast cancer, among those 18-45 years of age, was characterized in the Ontario Environment and Health Study (OEHS). The OEHS was a population-based case-control study undertaken in Ontario, Canada between 2013 and 2015. Primary incident breast cancers were identified within 3 months of diagnosis, and a population-based series of controls were recruited. Concentrations of ambient PAHs, using fluoranthene as a surrogate, were derived using a chemical transport model at a 2.5 km spatial resolution. These estimates were assigned to participants' residences at the time of the interview and 5 years prior. Logistic regression was used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) based on a quartile categorization of fluoranthene exposure while adjusting for a series of individual- and area-level risk factors. The shape of the exposure-response trend was evaluated using cubic splines. Results: Median fluoranthene exposure for cases and controls was 0.0017 mu g/m3 and 0.0014 mu g/m3, respectively. In models adjusted for a parsimonious set of risk factors, the highest quartile of exposure was associated with an increased risk of breast cancer (OR = 2.16; 95% CI = 1.22, 3.84). Restricted spline analyses revealed nonlinear dose-response patterns. Conclusions: These findings support the hypothesis that ambient PAH exposures increases the risk of early-onset breast cancer. https://doi.org/10.1097/ee9.0000000000000333

Persistent endocrine-disrupting chemicals and incident uterine leiomyomata: A mixtures analysis,
Wesselink, A. K., Henn, B. C., Fruh, V., Geller, R. J., Coleman, C. M., Schildroth, S., Sjodin, A., Bethea, T. N., Noel, N. L., Baird, D. D., Wegienka, G. and Wise, L. A., *Science of the Total Environment*, Nov 2024, Vol. 951.

Background: Uterine leiomyomata (UL; fibroids) are hormone-dependent neoplasms that can cause significant gynecologic morbidity. Studies have documented associations between concentrations of persistent endocrinedisrupting chemicals (EDCs) and UL incidence; however, few have assessed the effects of EDC mixtures on UL. Methods: In the Study of Environment, Lifestyle, and Fibroids, a prospective cohort study, participants attended study visits at baseline and approximately every 20 months for up to 10 years; at each visit, they completed questionnaires, provided blood samples, and underwent standardized ultrasound examinations. In baseline plasma samples (n = 1155), we quantified concentrations of polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and organochlorine pesticides using high-resolution mass spectrometry. We selected nine EDCs detected in >60 % of samples (4 PCBs, 4 PBDEs, and 2,2-bis(4-chlorophenyl)-1,1-dichloroethene (p,p'DDE)) and conducted probit Bayesian kernel machine regression with hierarchical variable selection to estimate effects of the EDC mixture and individual EDCs on UL incidence, adjusting for potential confounders. Results: During 10 years of follow-up, 32 % of participants

developed ultrasound-detected UL. The EDC mixture was not appreciably associated with the probit of UL ((3 comparing all EDCs at their 75th vs. 50th percentile:= 0.01, 95 % credible interval [CrI]: -0.11, 0.10). However, individual EDC concentrations were associated with UL in opposing directions: PCB138/158 was positively associated with UL ((3 for 25th-to-75th-percentile increase when all other chemicals were set to their 50th percentile = 0.18, 95 % CrI: -0.09, 0.44), whereas PBDE99 and p,p'-DDE were inversely associated with UL ((3 = -0.06, 95 % CrI: -0.21, 0.10 and (3 = -0.12, 95 % CrI: -0.34, 0.10, respectively). There was little evidence of interaction between EDCs. Conclusion: In this prospective ultrasound study, a mixture of persistent EDCs was not appreciably associated with incident UL during 10 years of follow-up, but individual EDCs were associated with UL in opposite directions. https://doi.org/10.1016/j.scitotenv.2024.175871

Association between pre- and postnatal exposure to endocrine-disrupting chemicals and birth and neurodevelopmental outcomes: an extensive review,
Yesildemir, O. and Celik, M. N., *Clinical and Experimental Pediatrics*, Jul 2024, Vol. 67, no. 7, p. 328-346.

Endocrine-disrupting chemicals (EDCs) are natural or synthetic chemicals that mimic, block, or interfere with the hormones in the body. The most common and well-studied EDCs are bisphenol A, phthalates, and persistent organic pollutants including polychlorinated biphenyls, polybrominated diphenyl ethers, per- and polyfluoroalkyl substances, other brominated flame retardants, organochlorine pesticides, dioxins, and furans. Starting in embryonic life, humans are constantly exposed to EDCs through air, diet, skin, and water. Fetuses and newborns undergo crucial developmental processes that allow adaptation to the environment throughout life. As developing organisms, they are extremely sensitive to low doses of EDCs. Many EDCs can cross the placental barrier and reach the developing fetal organs. In addition, newborns can be exposed to EDCs through breastfeeding or formula feeding. Pre- and postnatal exposure to EDCs may increase the risk of childhood diseases by disrupting the hormone-mediated processes critical for growth and development during gestation and infancy. This review discusses evidence of the relationship between pre- and postnatal exposure to several EDCs, childbirth, and neurodevelopmental outcomes. Available evidence suggests that pre- and postnatal exposure to certain EDCs causes fetal growth restriction, preterm birth, low birth weight, and neurodevelopmental problems through various mechanisms of action. Given the adverse effects of EDCs on child development, further studies are required to clarify the overall associations. https://doi.org/10.3345/cep.2023.00941

Phthalate exposure as a hidden risk factor for uterine leiomyoma in adult women: Accumulated evidence from observational studies,
Zhang, H., Zhou, H. L., Chen, X. W., Guo, H. T., Lin, Q. and Chen, X. Q., *Ecotoxicology and Environmental Safety*, Oct 2024, Vol. 285.

Background: There is evidence that exposure to phthalate in women may increase the risk of uterine leiomyomas. Whereas, the association between exposure to phthalate and the incidence of uterine leiomyoma remained inconclusive. Methods: A meta-analysis was performed to evaluate their relationship. Literature eligible for inclusion was found in PubMed, EMBASE, Web of Science, and WanFang Medical Database. Pooled odds ratio (OR) with 95 % confidence interval (CI) was calculated to assess the risk for effect estimate for each phthalate. Results: A total of fourteen observational studies with 5777 subjects of adult women were included in this study. In the pooled analysis, we found an elevated risk of uterine leiomyoma among women who were exposed to higher levels of di-2-ethylhexyl phthalate (DEHP) (OR 1.61, 95 % CI: 1.18-2.20), as estimated indirectly from the molar summation of its urinary metabolite concentrations. In addition, a positive association was observed between the occurrence of uterine leiomyoma and exposure to low molecular weight phthalate mixture (OR 1.08, 95 % CI: 1.00-1.15), as well as high molecular weight phthalate mixture (OR 1.08, 95 % CI: 1.01-1.15), as quantified by integrating the effect estimates of individual metabolite from each study. Urinary levels of DEHP metabolites, monobenzyl phthalate, mono-(3-carboxypropyl) phthalate, mono-isobutyl phthalate, mono-n-butyl phthalate, monoethyl phthalate, and monomethyl phthalate were not appreciably correlated with the risk of uterine leiomyoma. Conclusion: Our results indicated that exposure to DEHP, and co-exposure to high or low molecular weight phthalate mixture might be potential risk factors for uterine leiomyoma in adult women. Owing to the indirect estimation of association, when interpreting these findings, cautions should be taken. https://doi.org/10.1016/j.ecoenv.2024.117069

Association between phthalates exposure and non-alcoholic fatty liver disease under different diagnostic criteria: a cross-sectional study based on NHANES 2017 to 2018,
Zou, J. Z., Gu, Q. D. and Gu, D. Y., *Frontiers in Public Health*, Sep 2024, Vol. 12.

Purpose Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease. Phthalates have been suggested to influence the development of NAFLD due to their endocrine-disrupting properties, but studies based on nationally representative populations are insufficient, and existing studies seem to have reached conflicting conclusions. Due to changes in legislation, the use of traditional phthalates has gradually decreased, and the phthalates substitutes is getting more attention. This study aims to delve deeper into how the choice of diagnostic approach influences observed correlations and concern about more alternatives of phthalates, thereby offering more precise references for the prevention and treatment of NAFLD.Methods A cohort of 641 participants, sourced from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 database, was evaluated for NAFLD using three diagnostic methods: the Hepatic Steatosis Index (HSI), the US Fatty Liver Indicator (US.FLI), and Vibration Controlled Transient Elastography (VCTE). The urinary metabolite concentrations of Di-2-ethylhexyl phthalate (DEHP), Di-isodecyl phthalate (DIDP), Di-isononyl phthalate (DINP), Di-n-butyl phthalate (DnBP), Di-isobutyl phthalate (DIBP), Di-ethyl phthalate (DEP) and Di-n-octyl phthalate (DnOP) were detected. The association between NAFLD and urinary phthalate metabolites was evaluated through univariate and multivariate logistic regression analyses, considering different concentration gradients of urinary phthalates.Results Univariate logistic regression analysis found significant correlations between NAFLD and specific urinary phthalate metabolites, such as Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), Mono-2-ethyl-5-carboxypentyl phthalate (MECPP), and Mono-(carboxyisoctyl) phthalate (MCiOP), across different diagnostic criteria. In a multivariate logistic regression analysis adjusting only for demographic data, MEOHP (OR = 3.26, 95% CI = 1.19-8.94, p = 0.029), MEHHP (OR = 3.98, 95% CI = 1.43-11.1, p = 0.016), MECPP (OR = 3.52, 95% CI = 1.01-12.2, p = 0.049), and MCiOP (OR = 4.55, 95% CI = 1.93-10.7, p = 0.005) were positively related to NAFLD defined by HSI and VCTE. The correlation strength varied with the concentration of phthalates, indicating a potential dose-response relationship. Adjusting for all covariates in multivariate logistic regression, only MCiOP (OR = 4.22, 95% CI = 1.10-16.2, p = 0.044), as an oxidative metabolite of DINP, remained significantly associated with NAFLD under the VCTE criterion, suggesting its potential role as a risk factor for NAFLD.Conclusion This research highlights a significant association between DINP and NAFLD. These findings underscore the need for further investigation into the role of the phthalates substitutes in the pathogenesis of NAFLD and the importance of considering different diagnostic criteria in research. https://doi.org/10.3389/fpubh.2024.1407976

Toxicité sur l'homme

The dark side of beauty: an in-depth analysis of the health hazards and toxicological impact of synthetic cosmetics and personal care products,
Alnuqaydan, A. M., *Frontiers in Public Health*, Aug 2024, Vol. 12.

Over the past three decades, the popularity of cosmetic and personal care products has skyrocketed, largely driven by social media influence and the propagation of unrealistic beauty standards, especially among younger demographics. These products, promising enhanced appearance and self-esteem, have become integral to contemporary society. However, users of synthetic, chemical-based cosmetics are exposed to significantly higher risks than those opting for natural alternatives. The use of synthetic products has been associated with a variety of chronic diseases, including cancer, respiratory conditions, neurological disorders, and endocrine disruption. This review explores the toxicological impact of beauty and personal care products on human health, highlighting the dangers posed by various chemicals, the rise of natural ingredients, the intricate effects of chemical mixtures, the advent of nanotechnology in cosmetics, and the urgent need for robust regulatory measures to ensure safety. The paper emphasizes the necessity for thorough safety assessments, ethical ingredient sourcing, consumer education, and collaboration between governments, regulatory bodies, manufacturers, and consumers. As we delve into the latest discoveries and emerging trends in beauty product regulation and safety, it is clear that the protection of public health and well-being is a critical concern in this ever-evolving field. https://doi.org/10.3389/fpubh.2024.1439027

The Effects of Endocrine Disruptors on Adolescent Health,
Altikardesler, O. K. and Bas, F., *Journal of Child - Cocuk Dergisi*, 2023, Vol. 23, no. 2, p. 171-178.

Endocrine disrupting chemicals are found in many products such as soaps, shampoos, perfumes, kitchenware, textile materials, plastic bottles and containers, toys, and even foods and drinking water. These chemicals can enter the body through digestion, skin absorption, inhalation, and breast milk, as well as transplacentally.

Although restrictions have been placed on the use of some chemicals, exposure continues due to the reintroduction of similar chemicals and the ability of certain chemicals to remain in the environment or in food chains for a long time. Endocrine disruptors can even cause intergenerational effects, and studies have shown them to have negative effects on many bodily systems. Hormone-related cancers such as of the breast and prostate, as well as diabetes, obesity, precocious puberty, hormone level changes, being prone to infections, autoimmune diseases, asthma, attention-deficit/hyperactivity disorder, and learning difficulties, are some of the negative health consequences they cause. Genetic and environmental factors play a role in the development of certain endocrine disorders and cancers, and their increase over the years has drawn attention to how exposure to endocrine disruptors contributes to this situation. This review article examines the effects of endocrine disrupting chemicals such as phytoestrogens, bisphenol A, phthalates, perfluoroalkyl substances (PFAS), dioxins, and polychlorinated biphenyls (PCBs) on adolescent health in light of current studies. Taking precautions regarding exposure levels will help reduce the negative effects these chemicals have on adolescent health. https://doi.org/10.26650/jchild.2023.950386

Is it time to revise the fighting strategy toward type 2 diabetes? Sex and pollution as new risk factors, Barbieri, M., Prattichizzo, F., La Grotta, R., Matacchione, G., Scisciola, L., Fontanella, R. A., Tortorella, G., Benedetti, R., Carafa, V., Marfella, R., Ceriello, A. and Paolisso, G., *Ageing Research Reviews*, Aug 2024, Vol. 99.

Diabetes mellitus, a metabolic condition affecting around 537 million individuals worldwide, poses significant challenges, particularly among the elderly population. The etiopathogenesis of type 2 diabetes (T2D) depends on a combination of the effects driven by advancing age, genetic background, and lifestyle habits, e.g. . overnutrition. These factors influence the development of T2D differently in men and women, with an obvious sexual dimorphism possibly underlying the diverse clinical features of the disease in different sexes. More recently, environmental pollution, estimated to cause 9 million deaths every year, is emerging as a novel risk factor for the development of T2D. Indeed, exposure to atmospheric pollutants such as PM2.5, 2.5 , O3, 3 , NO2, 2 , and Persistent Organic Pollutants (POP)s, along with their combination and bioaccumulation, is associated with the development of T2D and obesity, with a 15 % excess risk in case of exposure to very high levels of PM2.5. 2.5 . Similar data are available for plasticizer molecules, e.g. . bisphenol A and phthalates, emerging endocrine-disrupting chemicals. Even though causality is still debated at this stage, preclinical evidence sustains the ability of multiple pollutants to affect pancreatic function, promote insulin resistance, and alter lipid metabolism, possibly contributing to T2D onset and progression. In addition, preclinical findings suggest a possible role also for plastic itself in the development of T2D. Indeed, pioneeristic studies evidenced that micro- or nanoplastics (MNP)s, particles in the micro- or nano- range, promote cellular damage, senescence, inflammation, and metabolic disturbances, leading to insulin resistance and impaired glucose metabolism in animal and/or in vitro models. Here we synthesize recent knowledge relative to the association between air-related or plastic-derived pollutants and the incidence of T2D, discussing also the possible mechanistic links suggested by the available literature. We then anticipate the need for future studies in the field of candidate therapeutic strategies limiting pollution-induced damage in preclinical models, such as SGLT-2 inhibitors. We finally postulate that future guidelines for T2D prevention should consider pollution and sex an additional risk factors to limit the diabetes pandemic. https://doi.org/10.1016/j.arr.2024.102405

Dietary Exposure to Pesticide and Veterinary Drug Residues and Their Effects on Human Fertility and Embryo Development: A Global Overview,
Colopi, A., Guida, E., Cacciotti, S., Fuda, S., Lampitto, M., Onorato, A., Zucchi, A., Balistreri, C. R., Grimaldi, P. and Barchi, M., *International Journal of Molecular Sciences*, Aug 2024, Vol. 25, no. 16.

Drug residues that contaminate food and water represent a serious concern for human health. The major concerns regard the possible irrational use of these contaminants, since this might increase the amplitude of exposure. Multiple sources contribute to the overall exposure to contaminants, including agriculture, domestic use, personal, public and veterinary healthcare, increasing the possible origin of contamination. In this review, we focus on crop pesticides and veterinary drug residues because of their extensive use in modern agriculture and farming, which ensures food production and security for the ever-growing population around the world. We discuss crop pesticides and veterinary drug residues with respect to their worldwide distribution and impacts, with special attention on their harmful effects on human reproduction and embryo development, as well as their link to epigenetic alterations, leading to intergenerational and transgenerational diseases. Among the contaminants, the most commonly implicated in causing such disorders are organophosphates, glyphosate and antibiotics, with tetracyclines being the most frequently reported. This review highlights the importance of finding new management strategies for pesticides and veterinary drugs. Moreover, due to the still limited

knowledge on inter- and transgenerational effects of these contaminants, we underlie the need to strengthen research in this field, so as to better clarify the specific effects of each contaminant and their long-term impact. https://doi.org/10.3390/ijms25169116

Short-Term Exposure to Foodborne Xenoestrogens Affects Breast Cancer Cell Morphology and Motility Relevant for Metastatic Behavior In Vitro,
Del Favero, G., Bergen, J., Palm, L., Fellinger, C., Matlaeva, M., Szabadi, A., Fernandes, A. S., Saraiva, N., Schröder, C. and Marko, D., *Chemical Research in Toxicology*, Sep 2024, Vol. 37, no. 10, p. 1634-1650.

Breast cancer is highly susceptible to metastasis formation. During the time of disease progression, tumor pathophysiology can be impacted by endogenous factors, like hormonal status, as well as by environmental exposures, such as those related to diet and lifestyle. New lines of evidence point toward a potential role for foodborne endocrine disruptive chemicals in this respect; however, mechanistic understanding remains limited. At the molecular level, crucial steps toward metastasis formation include cell structural changes, alteration of adhesion, and reorganization of cytoskeletal proteins involved in motility. Hence, this study investigates the potential of dietary xenoestrogens to impact selected aspects of breast cancer cell mechanotransduction. Taking the onset of the metastatic cascade as a model, experiments focused on cell-matrix adhesion, single-cell migration, and adaptation of cell morphology. Dietary mycoestrogens alternariol (AOH, 1 mu M) and alpha-zearalenol (alpha-ZEL, 10 nM), soy isoflavone genistein (GEN, 1 mu M), and food packaging plasticizer bisphenol A (BPA, 10 nM) were applied as single compounds or in mixtures. Pursuing the hypothesis that endocrine active molecules could affect cell functions beyond the estrogen receptor-dependent cascade, experiments were performed comparing the MCF-7 cell line to the triple negative breast cancer cells MDA MB-231. Indeed, the four compounds functionally affected the motility and the adhesion of both cell types. These responses were coherent with rearrangements of the actin cytoskeleton and with the modulation of the expression of integrin beta 1 and cathepsin D. Mechanistically, molecular dynamics simulations confirmed a potential interaction with fragments of the alpha 1 and beta 1 integrin subunits. In sum, dietary xenoestrogens proved effective in modifying the motility and adhesion of breast cancer cells, as predictive end points for metastatic behavior in vitro. These effects were measurable after short incubation times (1 or 8 h) and contribute to shed novel light on the activity of compounds with hormonal mimicry potential in breast cancer progression. https://doi.org/10.1021/acs.chemrestox.4c00061

The alarming link between environmental microplastics and health hazards with special emphasis on cancer,
Goswami, S., Adhikary, S., Bhattacharya, S., Agarwal, R., Ganguly, A., Nanda, S. and Rajak, P., *Life Sciences*, Oct 2024, Vol. 355.

Microplastic contamination is a burgeoning environmental issue that poses serious threats to animal and human health. Microplastics enter the human body through nasal, dermal, and oral routes to contaminate multiple organs. Studies have advocated the existence of microplastics in human breast milk, sputum, faeces, and blood. Microplastics can find their ways to the sub-cellular moiety via active and passive approaches. At cellular level, microplastics follow clathrin and caveolae-dependent pathways to invade the sub-cellular environment. These environmental contaminants modulate the epigenetic control of gene expression, status of inflammatory mediators, redox homeostasis, cell-cycle proteins, and mimic the endocrine mediators like estrogen and androgen to fuel carcinogenesis. Furthermore, epidemiological studies have suggested potential links between the exposure to microplastics and the onset of various chronic diseases. Microplastics trigger uncontrolled cell proliferation and ensue tissue growth leading to various cancers affecting the lungs, blood, breasts, prostate, and ovaries. Additionally, such contamination can potentially affect sub-cellular signaling and injure multiple organs. In essence, numerous reports have claimed microplastic-induced toxicity and tumorigenesis in human and model animals. Nonetheless, the underlying molecular mechanism is still elusive and warrants further investigations. This review provides a comprehensive analysis of microplastics, covering their sources, chemistry, human exposure routes, toxicity, and carcinogenic potential at the molecular level. https://doi.org/10.1016/j.lfs.2024.122937

Novel insights into the role of bisphenol A (BPA) in genomic instability,
Hale, A. and Moldovan, G. L., *Nar Cancer*, Sep 2024, Vol. 6, no. 3.

Bisphenol A (BPA) is a phenolic chemical that has been used for over 50 years in the manufacturing of polycarbonate and polyvinyl chloride plastics, and it is one of the highest volume chemicals produced worldwide. Because BPA can bind to and activate estrogen receptors, studies have mainly focused on the

effect of BPA in disrupting the human endocrine and reproductive systems. However, BPA also plays a role in promoting genomic instability and has been associated with initiating carcinogenesis. For example, it has been recently shown that exposure to BPA promotes the formation of single stranded DNA gaps, which may be associated with increased genomic instability. In this review, we outline the mechanisms by which BPA works to promote genomic instability including chromosomal instability, DNA adduct formation, ROS production, and estrogen receptor (ER) activation. Moreover, we define the ways in which BPA promotes both carcinogenesis and resistance to chemotherapy, and we provide critical insights into future directions and outstanding questions in the field. https://doi.org/10.1093/narcan/zcae038

Human skin absorption of three plasticizers: Diisononyl-1,2-cyclohexanedicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHTP), and di(2-ethylhexyl) adipate (DEHA),
Hopf, N. B., De Luca, H. P., Koch, H. M., Pälmke, C., Berthet, A. and Reale, E., *Toxicology Letters*, Oct 2024, Vol. 400, p. 104-112.

*Alternative plasticizers such as diisononyl-1,2-cyclohexanedicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHTP), and di(2-ethylhexyl) adipate (DEHA) are progressively replacing phthalates in many consumer and professional products because of adverse effects on reproduction associated with some phthalates. Human exposures to these phthalate substitutes can occur through ingestion, skin absorption and inhalation. Skin uptake can lead to greater concentration at the target organs compared to ingestion because the skin exposure route bypasses the first-pass effect. Skin absorption studies are almost absent for these alternative plasticizers. We therefore wanted first, to characterize skin absorption of a mixture containing DINCH, DEHA and DEHTP in vitro using a flow-through diffusion cell system with ex vivo human skin, quantifying their respective monoester metabolites (mono-isononyl-cyclohexane-1,2-dicarboxylate (MINCH), mono-2-ethylhexyl adipate (MEHA), mono-2-ethylhexyl terephthalate (MEHTP), respectively); second, to validate these results by exposing five human volunteers to this mixture on their forearm and quantifying the corresponding urinary metabolites (including the monoesters and their oxidation products). Our study showed that two of these alternative plasticizers, DEHTP and DINCH, did not permeate skin showing as quantifiable metabolite levels in vitro and only traces of DEHA were quantified as its monoester metabolite, MEHA. Permeation coefficient (Kp) 0.06 and 55.8*10-7 cm/h for neat and emulsified DEHA, respectively, while the permeation rate (J) remained low for both (0.005 and 0.001 mu g/cm2/h, respectively). Participants exposed to a mixture of these three plasticizers did not have noteworthy urinary concentrations of their respective metabolites after 24 hours post-application. However, the alternative plasticizer mixture was completely absorbed after six hours post-application on the forearms of the human volunteers, and the urinary elimination curves showed a slight increase after 24 hours postapplication. Further studies on skin absorption of these substances should follow the urinary elimination kinetics of these metabolites more than 24 hours post-application. We also recommend quantifying the parent compounds in the in vitro diffusion experiments.* https://doi.org/10.1016/j.toxlet.2024.08.002

Specific and potent inhibition of steroid hormone pre-receptor regulator AKR1C2 by perfluorooctanoic acid: Implications for androgen metabolism,
Huacachino, A. A., Chung, A., Sharp, K. and Penning, T. M., *J Steroid Biochem Mol Biol*, Nov 20 2024, Vol. 246, p. 106641.

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous environmental pollutants that are highly stable synthetic organofluorine compounds. One congener perfluorooctanoic acid (PFOA) can be detected in nearly all humans and is recognized as an endocrine disrupting chemical (EDC). EDCs disrupt hormone synthesis and metabolism and receptor function. One mechanism of steroid hormone action is the pre-receptor regulation of ligand access to steroid hormone receptors by aldo-keto reductases. Here we report PFOA inhibition of AKR family 1 member C2 (AKR1C2), leading to dysregulation of androgen action. Spectrofluorimetric inhibitor screens identified PFOA as a competitive and tight binding inhibitor of AKR1C2, whose role is to inactivate 5α-dihydrotestosterone (5α-DHT). Further site directed mutagenesis studies along with molecular docking simulations revealed the importance of residue Valine 54 in mediating AKR1C2 inhibitor specificity. Binding site restrictions were explored by testing inhibition of other related PFAS chemicals, confirming that steric hinderance is a key factor. Furthermore, radiochromatography using HPLC and in line radiometric detection confirmed the accumulation of 5α-DHT as a result of PFOA inhibition of AKR1C2. We showed that PFOA could enhance the transactivation of AR in reporter genes assays in which 5α-DHT metabolism was blocked by AKR1C2 inhibition in HeLa cells. Taken together, these data suggest PFOA has a role in disrupting androgen action through inhibiting AKR1C2. Our work identifies an EDC function for PFOA not previously revealed. https://doi.org/10.1016/j.jsbmb.2024.106641

The effects of perfluorooctanoic acid on breast cancer metastasis depend on the phenotypes of the cancer cells: An in vivo study with zebrafish xenograft model,
Huang, C., Murgulet, I., Liu, L. D., Zhang, M. N., Garcia, K., Martin, L. and Xu, W., *Environmental Pollution*, Dec 2024, Vol. 362.

Per- and polyfluorinated substances (PFAS) have been associated with numerous human diseases. Recent in vitro studies have implicated the association of PFAS with an increased risk of breast cancer in humans. This study aimed to assess the toxic effects of PFAS during the development of human breast cancer using a zebrafish xenograft model. Perfluorooctanoic acid (PFOA) was used as a PFAS chemical of interest for this study. Two common breast cancer cell lines, MCF-7 and MDA-MB-231, were used to represent the diversity of breast cancer phenotypes. Human preadipocytes were co-implanted with the breast cancer cells into the zebrafish embryos to optimize the microenvironment for tumor cells in vivo. With this modified model, we evaluated the potential effects of the PFOA on the metastatic potential of the two types of breast cancer cells. The presence of human preadipocytes resulted in an enhancement to the metastasis progress of the two types of cells, including the promotion of cell in vivo migration and proliferation, and the increased expression levels of metastatic biomarkers. The enhancement of MCF-7 proliferation by preadipocytes was observed after 2 days post injection (dpi) while the increase of MDA-MB-231 proliferation was seen after 6 dpi. The breast cancer metastatic biomarkers, cadherin 1 (cdh1), and small breast epithelial mucin (sbem) genes demonstrated significant down- and upregulations respectively, by the co-injection of preadipocytes. In the optimized xenograft model, the PFOA consistently promoted cell proliferation and migration and altered the metastatic biomarker expression in MCF-7, which suggested a metastatic effect of PFOA on MCF-7. However, those effects were not consistently observed in MDA-MB-231. The presence of the preadipocytes in the xenograft model may provide a necessary microenvironment for the progress of tumor cells in zebrafish embryos. The finding suggested that the impacts of PFOA exposure on different phenotypes of breast cancers may differ. https://doi.org/10.1016/j.envpol.2024.124975

Identification of endocrine-disrupting chemicals targeting key OP-associated genes via bioinformatics and machine learning,
Huang, X. Z., Huang, H., Chen, H. and Wei, Y. K., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 286.

Osteoporosis (OP), a metabolic disorder predominantly impacting postmenopausal women, has seen considerable progress in diagnosis and treatment over the past few decades. However, the intricate interplay between genetic factors and endocrine disruptors (EDCs) in the pathogenesis of OP remains inadequately elucidated. The objective of this research is to examine the environmental pollutants and their regulatory mechanisms that could potentially influence the pathogenesis of OP, in order to establish a theoretical foundation for the targeted prevention and medical management of individuals with OP. Utilizing CTD and GEO datasets, network toxicology and bioinformatics analyses were conducted to identify target genes from a pool of 98 co-associated genes. Subsequently, a novel prediction model was developed employing a multiple machine learning algorithm. The efficacy of the model was validated based on the area under the receiver operating characteristic curve. Finally, real-time quantitative polymerase chain reaction (qRT-PCR) was used to confirm the expression levels of key genes in clinical samples. We have identified significant genes (FOXO3 and LUM) associated with OP and conducted Gene Ontology, Kyoto Encyclopedia of Genes and Genomes enrichment analysis, immune infiltration analysis, and molecular docking analysis. Through the analysis of these key genes, we have identified 13 EDCs that have the potential to impact OP. Several endocrine disruptors, such as Dexamethasone, Perfluorononanoic acid, genistein, cadmium, and bisphenol A, have been identified as notable environmental pollutants that impact the OP. Molecular docking analysis revealed significant binding affinity of major EDCs to the post-translational protein structures of key genes. This study demonstrates that EDCs, including dexamethasone, perfluorononanoic acid, genistein, cadmium, and bisphenol A, can be identified as important environmental pollutants affecting OP, and that FOXO3 and LUM have the potential to be diagnostic markers for OP. These results elucidate a novel association between EDCs regulated by key genes and the onset of OP. https://doi.org/10.1016/j.ecoenv.2024.117155

An in vitro approach reveals molecular mechanisms underlying endocrine disruptor-induced epimutagenesis,
Lehle, J. D., Lin, Y. H., Gomez, A., Chavez, L. and Mccarrey, J. R., *Elife*, Oct 2024, Vol. 13.

Endocrine disrupting chemicals (EDCs) such as bisphenol S (BPS) are xenobiotic compounds that can disrupt endocrine signaling due to steric similarities to endogenous hormones. EDCs have been shown to induce disruptions in normal epigenetic programming (epimutations) and differentially expressed genes (DEGs) that predispose disease states. Most interestingly, the prevalence of epimutations following exposure to many EDCs persists over multiple generations. Many studies have described direct and prolonged effects of EDC exposure in animal models, but many questions remain about molecular mechanisms by which EDC-induced epimutations are introduced or subsequently propagated, whether there are cell type-specific susceptibilities to the same EDC, and whether this correlates with differential expression of relevant hormone receptors. We exposed cultured pluripotent (iPS), somatic (Sertoli and granulosa), and primordial germ cell-like (PGCLC) cells to BPS and found that differential incidences of BPS-induced epimutations and DEGs correlated with differential expression of relevant hormone receptors inducing epimutations near relevant hormone response elements in somatic and pluripotent, but not germ cell types. Most interestingly, we found that when iPS cells were exposed to BPS and then induced to differentiate into PGCLCs, the prevalence of epimutations and DEGs was largely retained, however, >90% of the specific epimutations and DEGs were replaced by novel epimutations and DEGs. These results suggest a unique mechanism by which an EDC-induced epimutated state may be propagated transgenerationally. https://doi.org/10.7554/eLife.93975

p,p'-DDT induces apoptosis in human endometrial stromal cells via the PI3K/AKT pathway and oxidative stress,
Oh, S. R., Bin Park, S. and Cho, Y. J., *Clinical and Experimental Reproductive Medicine-Cerm*, Sep 2024, Vol. 51, no. 3, p. 247-259.

Objective: Bis-[4-chlorophenyl]-1,1,1-trichloroethane (DDT), one of the most widely used synthetic pesticides, is an endocrine-disrupting chemical with the potential to interfere with the human reproductive system. The effects of DDT and one of its metabolites, p,p'-DDT, '-DDT, on human endometrial stromal cells (ESCs) and health outcomes remain unknown. In this study, we investigated whetherp,p'-DDT p,p'-DDT induces an imbalance in cell proliferation and apoptosis in human ESCs via oxidative stress. Methods: We assessed apoptosis in ESCs by quantifying the expression of markers associated with both intrinsic and extrinsic pathways. Additionally, we measured levels of reactive oxygen species (ROS), antioxidant enzyme activity, and estrogen receptors (ERs). We also examined changes in signaling involving nuclear factor kappa-light-chain-enhancer of activated B cells. Results: Following treatment with 1,000 pg/mL of p,p'-DDT, we observed an increase in Bax expression, a decrease in Bcl-2 expression, and increases in the expression of caspases 3, 6, and 8. We also noted a rise in the generation of ROS and a reduction in glutathione peroxidase expression after treatment with p,p'-DDT. '-DDT. Additionally, p,p'-DDT '-DDT treatment led to changes in ER expression and increases in the protein levels of phosphatidylinositol 3-kinase (PI3K), phospho-protein kinase B (phospho-AKT), and phospho-extracellular signal-regulated kinase (phospho-ERK). Conclusion:p,p'-DDT p,p '-DDT was found to induce apoptosis in human ESCs through oxidative stress and an ER-mediated pathway. The activation of the PI3K/AKT and ERK pathways could represent potential mechanisms by which p,p'-DDT '-DDT prompts apoptosis in human ESCs and may be linked to endometrial pathologies. https://doi.org/10.5653/cerm.2022.05792

Establishment of tumor microenvironment following bisphenol A exposure in the testis,
Park, Y. J., Pang, W. K., Hwang, S. M., Ryu, D., Rahman, M. S. and Pang, M. G., *Ecotoxicology and Environmental Safety*, Oct 2024, Vol. 285.

Although detrimental roles of bisphenol A (BPA) in xenoestrogen target organs, testis and epididymis, and male fertility are well-documented, disruption of the immune privilege system in the male reproductive tract following BPA exposure remains poorly understood. Therefore, this study aimed to explore the precise mechanisms of BPA in interfering immune privilege in the testis on RNA sequencing results. CD-1 male mice were daily treated noobserved-adverse-effect (NOAEL, 5 mg BPA/kg BW) and lowest-observed-adverse-effects (LOAEL, 50 mg BPA/kg BW) of BPA by oral gavage for 6 weeks. Following the LOAEL exposure, the expression of immune responseassociated transcripts was upregulated in the testis. Moreover, BPA switch the testicular microenvironment to tumor friendly through the recruitment of tumor associated macrophages (TAMs), which can produce both antiand pro-inflammatory cytokines, such as TNF-alpha, TLR2, IL-10, and CXCL9. Number of testicular blood vessels were approximately 2-times increased by upregulation of matrix metallopeptidase 2 in TAMs and upregulation of AR expression in the nucleus of Leydig cells. Moreover, we found that the tumor-supportive environment can also be generated even though NOAEL BPA concentration due to the individual's variability in cancer susceptibility. https://doi.org/10.1016/j.ecoenv.2024.117071

Association between the Exposure to Phthalates and the Risk of Endometriosis: An Updated Review, Ribeiro, B., Mariana, M., Lorigo, M., Oliani, D., Ramalhinho, A. C. and Cairrao, E., *Biomedicines*, Aug 2024, Vol. 12, no. 8.

Endometriosis is a chronic gynecological disease, primarily associated with pelvic pain and infertility, that affects approximately 10% of the women of reproductive age. Estrogen plays a central role in endometriosis, and there is growing evidence that endocrine disruptors, such as phthalates, may contribute to its development. This review aimed to determine whether there is a causal relationship between phthalate exposure and the development of endometriosis, as well as the possible effects of phthalates on fertility, by analyzing epidemiological data. After a literature search with a combination of specific terms on this topic, we found that although there are limitations to the current studies, there is a clear association between phthalate exposure and endometriosis. Phthalates can interfere with the cellular processes of the endometrium; specifically, they can bind to PPAR and ER-alpha and activate TGF-beta, promoting different signaling cascades that regulate the expression of specific target genes. This may lead to inflammation, invasion, cytokine alteration, increased oxidative stress, and impaired cell viability and proliferation, culminating in endometriosis. Nevertheless, future research is important to curb the progression and development of endometriosis, and strategies for prevention, diagnosis, and treatment are a priority. In this regard, public policies and recommendations to reduce exposure to phthalates and other endocrine disruptors should be promptly implemented. https://doi.org/10.3390/biomedicines12081932

Bisphenol a negatively impacts cellular vascularization processes related to early pregnancy, Romanelli, F., Zenclussen, A. C. and Meyer, N., *Febs Open Bio*, May 2024, Vol. 14, p. 46-46. <Go to https://febs.onlinelibrary.wiley.com/doi/10.1002/2211-5463.13792

Potential hazards of bisphenol A on the male reproductive system: Induction of programmed cell death in testicular cells,
Sadek, K. M., Khalifa, N. E., Alshial, E. E., Abdelnour, S. A., Mohamed, A. a. R. and Noreldin, A. E., *Journal of Biochemical and Molecular Toxicology*, Sep 2024, Vol. 38, no. 9.

A common industrial chemical known as bisphenol A (BPA) has been linked to endocrine disruption and can interfere with hormonal signaling pathways in humans and animals. This comprehensive review aims to explore the detrimental consequences of BPA on reproductive organ performance and apoptosis induction, shedding light on the emerging body of evidence from laboratory animal studies. Historically, most studies investigating the connection between BPA and reproductive tissue function have mainly leaned on laboratory animal models. These studies have provided crucial insights into the harmful effects of BPA on several facets of reproduction. This review consolidates an increasing literature that correlates exposure to BPA in the environment with a negative impact on human health. It also integrates findings from laboratory studies conducted on diverse species, collectively bolstering the mounting evidence that environmental BPA exposure can be detrimental to both humans and animals, particularly to reproductive health. Furthermore, this article explores the fundamental processes by which BPA triggers cell death and apoptosis in testicular cells. By elucidating these mechanisms, this review aids a deeper understanding of the complex interactions between BPA and reproductive tissues. A common industrial chemical known as bisphenol A (BPA) has been linked to endocrine disruption and is capable of interfering with hormonal signaling pathways in both humans and animals. This comprehensive review aims to explore the detrimental consequences of BPA on reproductive tissue performance and apoptosis induction, shedding light on the emerging body of evidence from both laboratory animal studies and epidemiological research. Historically, most studies investigating the connection between BPA and reproductive tissue function have mainly leaned on laboratory animal models. These studies have provided crucial insights into the harmful effects of BPA on several facets of reproduction. However, until recently, the number of epidemiological investigations examining the impacts of BPA on reproductive tissue performance and apoptosis induction in humans was limited. This review consolidates an increasing body of human literature that correlates exposure to BPA in the environment with negative effects on human health. It also integrates findings from laboratory studies conducted on diverse species, collectively bolstering the mounting evidence that environmental BPA exposure can be detrimental to both humans and animals, particularly in relation to reproductive health. Furthermore, this article explores the fundamental processes by which BPA triggers cell death and apoptosis in testicular cells. By elucidating these mechanisms, this review aids a deeper understanding of the complex interactions between BPA and reproductive tissues. image Apoptosis of the testicular cells occurs in both healthy and pathological situations. EDCs cause widespread germ cell death by upregulating apoptosis-related proteins or causing an oxidative imbalance Classifying the environmental pollutants that pose a significant risk to people in general and selecting the factors that need

more investigation could aid in discovering environmental contaminants' risks. https://doi.org/10.1002/jbt.23844

Pyrethroids and reproductive function: some endocrine disrupting perspectives from molecular simulations,
Sheikh, I. A., Beg, M. A. and Macha, M. A., *Ecotoxicology*, Nov 2024, Vol. 33, no. 9, p. 1086-1095.

Pyrethroids are widely used insecticides with huge applications for household as well as agricultural purposes and contribute to improved product quality and higher yields. In recent decades, the demand for pyrethroids has increased significantly due to advantages such as broad-spectrum efficacy, high insecticidal potential, and lower pest resistance. However, several studies have suggested that human exposure to pyrethroids leads to reproductive problems. Sex hormone-binding globulin (SHBG) is an important hormone transport protein regulating the availability of steroids at their target site. The aim of our study was to investigate the structural interactions of commonly used pyrethroids, cypermethrin and deltamethrin, with ligand binding pocket of SHBG. Cypermethrin and deltamethrin were docked into the steroid binding pocket of SHBG using Schrodinger's induced fit docking (IFD) followed by molecular dynamics (MD) simulation studies. The resultant SHBG-pyrethroid complexes from IFD experiments were subjected to structural analysis including the molecular interactions followed by binding energy estimation. The analysis revealed that both the ligands were tightly bound in the SHBG pocket with high percentage of commonality among the SHBG residues between the indicated pyrethroid ligands and the SHBG native ligand, dihydrotestosterone (DHT). The estimated binding energy values for cypermethrin were less but close to the values calculated for the SHBG native ligand, DHT. However, the estimated binding energy values for deltamethrin were higher compared to the values calculated for SHBG native ligand, DHT. Furthermore, the MD simulation results also revealed the higher stability of SHBG-deltamethrin than SHBG-cypermethrin complex. To sum up, the results suggested that deltamethrin has a greater capability than cypermethrin to prevent sex steroid hormone from binding to SHBG, even though both pyrethroids have this ability. Consequently, this might hamper the circulatory transport of sex steroid hormones and their availability at the target site, subsequently interfering with reproductive function. https://doi.org/10.1007/s10646-024-02801-8

Which is the current knowledge on man-made endocrine- disrupting chemicals in follicular fluid? An overview of effects on ovarian function and reproductive health,
Shulhai, A. M., Bianco, V., Donini, V., Esposito, S. and Street, M. E., *Frontiers in Endocrinology*, Oct 2024, Vol. 15.

The increase in female reproductive disorders, such as polycystic ovary syndrome, endometriosis, and diminished ovarian reserve that lead to subfertility and infertility, has encouraged researchers to search and discover their underlying causes and risk factors. One of the crucial factors that may influence the increasing number of reproductive issues is environmental pollution, particularly exposure to man-made endocrine-disrupting chemicals (EDCs). EDCs can interfere with the ovarian microenvironment, impacting not only granulosa cell function but also other surrounding ovarian cells and follicular fluid (FF), which all play essential roles for oocyte development, maturation, and overall reproductive function. FF surrounds developing oocytes within an ovarian follicle and represents a dynamic milieu. EDCs are usually found in biological fluids, and FF is therefore of interest in this respect. This narrative review examines the current knowledge on specific classes of EDCs, including industrial chemicals, pesticides, and plasticizers, and their known effects on hormonal signaling pathways, gene expression, mitochondrial function, oxidative stress induction, and inflammation in FF. We describe the impact of EDCs on the development of reproductive disorders, oocyte quality, menstrual cycle regulation, and their effect on assisted reproductive technique outcomes. The potential transgenerational effects of EDCs on offspring through animal and first-human studies has been considered also. While significant progress has been made, the current understanding of EDCs' effects on ovarian function, particularly in humans, remains limited, underscoring the need for further research to clarify actions and effects of EDCs in the ovary. https://doi.org/10.3389/fendo.2024.1435121

Bisphenol A triggers activation of ocular immune system and aggravates allergic airway inflammation,
Ueda, T., Adachi, T., Hayashi, T., Yasuda, K., Matsushita, K., Koike, E., Yanagisawa, R., Nagatake, T., Kunisawa, J., Ishii, K. J., Tsuzuki, K. and Kuroda, E., *Clinical Immunology*, Nov 2024, Vol. 268.

Bisphenol A (BPA) is widely used in manufacturing plastic products, and it has been reported that exposure through the airway or orally aggravates allergic airway inflammation. Because BPA is detected in the atmosphere and indoor environments, the eyes can also be exposed to BPA. After ocular exposure to BPA

and antigen via eye drops, we observed enhanced antigen uptake of antigen-presenting cells (APCs) in tear duct-associated lymphoid tissue (TALT). Additionally, we observed the formation of germinal center (GC) B cells in TALT and induction of allergic airway inflammation in mice sensitized with BPA and antigen via eye drops, followed by airway antigen exposure. We also found that DNAX-activating protein of 12 kDa (DAP12)-deficient mice displayed impaired activation of APCs enhanced by ocular exposure to BPA. These results indicate that ocular sensitization to BPA and allergen triggers allergic inflammation via TALT activation, and that DAP12 might be a key molecule for modulating the ocular immune system. https://doi.org/10.1016/j.clim.2024.110370

Effects of polystyrene micro- and nanoplastics on androgen- and estrogen receptor activity and steroidogenesis in vitro,
Van Boxel, J., Khargi, R. R. J., Nijmeijer, S. M., Heinzelmann, M. T., Pereira, D. D., Lamoree, M. H. and Van Duursen, M. B. M., *Toxicology in Vitro*, Dec 2024, Vol. 101.

While many plastic additives show endocrine disrupting properties, this has not been studied for micro- and nanoplastics (MNPs) particles despite their ubiquitous presence in humans. The objective of this study was to determine the effects of various sizes and concentrations of polystyrene (PS)-MNPs (50-10,000 nm, 0.01-100 mu g/mL) on estrogen- and androgen receptor (ER and AR) activity and steroidogenesis in vitro. Fluorescent (F)PS-MNPs of <= 1000 nm were internalized in VM7 and H295R cells and FPS-MNPs <= 200 nm in AR-ecoscreen cells. H295R cells displayed the highest uptake and particles were closer to the nucleus than other cell types. None of the sizes and concentrations PS-MNPs tested affected ER or AR activity. In H295R cells, PS-MNPs caused some statistically significant changes in hormone levels, though these showed no apparent concentration or size-dependent patterns. Additionally, PS-MNPs caused a decrease in estriol (E3) with a maximum of 37.5 % (100 mu g/mL, 50 nm) and an increase in gene expression of oxidative stress markers GPX1 (1.26-fold) and SOD1 (1.23-fold). Taken together, our data show limited endocrine-disrupting properties of PS-MNPs in vitro. Nevertheless the importance of E3 in the placenta warrants further studies in the potential effects of MNPs during pregnancy. https://doi.org/10.1016/j.tiv.2024.105938

Reduced ovarian cholesterol and steroid biosynthesis along with increased inflammation are associated with high DEHP metabolite levels in human ovarian follicular fluids,
Varik, I., Zou, R. Y., Bellavia, A., Rosenberg, K., Sjunnesson, Y., Hallberg, I., Holte, J., Lenters, V., Van Duursen, M., Pedersen, M., Svingen, T., Vermeulen, R., Salumets, A., Damdimopoulou, P. and Velthut-Meikas, A., *Environment International*, Sep 2024, Vol. 191.

The plasticizer di(2-ethylhexyl) phthalate (DEHP) is known to have endocrine-disrupting properties mediated by its many metabolites that form upon exposure in biological systems. In a previous study, we reported an inverse association between DEHP metabolites in the human ovarian follicular fluid (FF) and the responsiveness of the follicles to controlled ovarian stimulation during in vitro fertilization (IVF) treatments. Here, we explored this association further through molecular analysis of the ovarian FF samples. Ninety-six IVF patients from Swedish (N = 48) and Estonian (N = 48) infertility clinics were selected from the previous cohort (N = 333) based on the molar sum of DEHP metabolites in their FF samples to arrive at "high" (mean 7.7 +/- SD 2.3 nM, N = 48) and "low" (0.8 +/- 0.4 nM, N = 48) exposure groups. Extracellular miRNA levels and concentrations of 15 steroid hormones were measured across FF samples. In addition, FF somatic cells, available for the Estonian patients, were used for RNA sequencing. Differential expression (DE) and interactions between miRNA and mRNA networks revealed that the expression levels of genes in the cholesterol biosynthesis and steroidogenesis pathways were significantly decreased in the high compared to the low DEHP group. In addition, the DE miRNAs were predicted to target key enzymes within these pathways (FDR < 0.05). A decreased 17-OH-progesterone to progesterone ratio was observed in the FF of the high DEHP group (p < 0.05). Additionally, the expression levels of genes associated with inflammatory processes were elevated in the FF somatic cells, and a computational cell-type deconvolution analysis suggested an increased immune cell infiltration into the high DEHP follicles (p < 0.05). In conclusion, elevated DEHP levels in FF were associated with a significantly altered follicular milieu within human ovaries, involving a pro-inflammatory environment and reduced cholesterol metabolism, including steroid synthesis. These results contribute to our understanding of the molecular mechanisms of female reprotoxic effects of DEHP. https://doi.org/10.1016/j.envint.2024.108960

Bisphenol F and Bisphenol S in a Complex Biomembrane: Comparison with Bisphenol A,
Villalaín, J., *Journal of Xenobiotics*, Sep 2024, Vol. 14, no. 3, p. 1201-1220.

Bisphenols are a group of endocrine-disrupting chemicals used worldwide for the production of plastics and resins. Bisphenol A (BPA), the main bisphenol, exhibits many unwanted effects. BPA has, currently, been replaced with bisphenol F (BPF) and bisphenol S (BPS) in many applications in the hope that these molecules have a lesser effect on metabolism than BPA. Since bisphenols tend to partition into the lipid phase, their place of choice would be the cellular membrane. In this paper, I carried out molecular dynamics simulations to compare the localization and interactions of BPA, BPF, and BPS in a complex membrane. This study suggests that bisphenols tend to be placed at the membrane interface, they have no preferred orientation inside the membrane, they can be in the monomer or aggregated state, and they affect the biophysical properties of the membrane lipids. The properties of bisphenols can be attributed, at least in part, to their membranotropic effects and to the modulation of the biophysical membrane properties. The data support that both BPF and BPS, behaving in the same way in the membrane as BPA and with the same capacity to accumulate in the biological membrane, are not safe alternatives to BPA. https://doi.org/10.3390/jox14030068

Multifaceted paternal exposures before conception and their epigenetic impact on offspring,
Wu, X. J., Zhang, W. P., Chen, H. J. and Weng, J. F., *Journal of Assisted Reproduction and Genetics*, 2024 Sep 2024.

As scientific research progresses, there is an increasing understanding of the importance of paternal epigenetics in influencing the health and developmental path of offspring. Prior to conception, the environmental exposures and lifestyle choices of fathers can significantly influence the epigenetic state of sperm, including DNA methylation and histone changes, among other factors. These alterations in epigenetic patterns have the potential for transgenerational transmission potential and may exert profound effects on the biological characteristics of descendants. Paternal epigenetic changes not only affect the regulation of gene expression patterns in offspring but also increase the risk to certain diseases. It is crucial to comprehend the conditions that fathers are exposed to before conception and the potential outcomes of these conditions. This understanding is essential for assessing personal reproductive decisions and anticipating health risks for future generations. This review article systematically summarizes and analyzes current research findings regarding how paternal pre-pregnancy exposures influence offspring as well as elucidates underlying mechanisms, aiming to provide a comprehensive perspective for an enhanced understanding of the impact that paternal factors have on offspring health. https://doi.org/10.1007/s10815-024-03243-1

Potential endocrine-disrupting effects of iprodione via estrogen and androgen receptors: evaluation using in vitro assay and an in silico model,
Yang, J. Y., Lim, J. H., Park, S. J., Jo, Y., Yang, S. Y., Paik, M. K. and Hong, S. H., *Applied Biological Chemistry*, Aug 2024, Vol. 67, no. 1.

This study was conducted to provide evidence, using in vitro and in silico testing methods, regarding the adverse effects of iprodione, a representative dichlorophenyl dicarboxamide fungicide, on the endocrine system. In the present study, we used the HeLa9903 stably transfected transactivation assay (OECD TG 455), 22Rv1/MMTV_GR-KO androgen receptor transcriptional activation assay (OECD TG 458), and toxicity prediction using VEGA QSAR. Our results showed that iprodione had no estrogen receptor antagonistic or androgen receptor agonistic effects; however, iprodione was determined to be an estrogen receptor agonist (log PC10 value is less than - 9) and androgen receptor antagonist (log IC30 value is - 4.58) without intrinsic toxicity against the human cell lines used in this study. VEGA QSAR was used to evaluate five substances with structures similar to that of iprodione. Among them, four chemicals were found to have positive androgen receptor and aromatase activities and have been observed to be developmental toxicants. These results suggest that iprodione regulates steroid hormone receptor interactions and is a potential reproductive toxicant. https://doi.org/10.1186/s13765-024-00932-4

Unveiling the impact of estrogen exposure on ovarian cancer: a comprehensive risk model and immune landscape analysis,
Yu, Z. N., Yang, W. L., Zhang, Q. W. and Zheng, M. Y., *Toxicology Mechanisms and Methods*, 2024 Sep 2024.

This study examines the impact of estrogenic compounds like bisphenol A (BPA), estradiol (E2), and zearalenone (ZEA) on human ovarian cancer, focusing on constructing a risk model, conducting gene set variation analysis (GSVA), and evaluating immune infiltration. Differential gene expression analysis identified 980 shared differentially expressed genes (DEGs) in human ovarian cells exposed to BPA, E2, and ZEA, indicating disruptions in ribosome biogenesis and RNA processing. Using the cancer genome atlas ovarian cancer (TCGA-OV) dataset, a least absolute shrinkage and selection operator (LASSO)-based risk model was

developed incorporating prognostic genes 4-hydroxyphenylpyruvate dioxygenase like (HPDL), Thy-1 cell surface antigen (THY1), and peptidase inhibitor 3 (PI3). This model effectively stratified ovarian cancer patients into high-risk and low-risk categories, showing significant differences in overall survival, disease-specific survival, and progression-free survival. GSVA analysis linked HPDL expression to pathways related to the cell cycle, DNA damage, and repair, while THY1 and PI3 were associated with apoptosis, hypoxia, and proliferation pathways. Immune infiltration analysis revealed distinct immune cell profiles for high and low-expression groups of HPDL, THY1, and PI3, indicating their influence on the tumor microenvironment. The findings demonstrate that estrogenic compounds significantly alter gene expression and oncogenic pathways in ovarian cancer. The risk model integrating HPDL, THY1, and PI3 offers a strong prognostic tool, with GSVA and immune infiltration analyses providing insights into the interplay between these genes and the tumor microenvironment, suggesting potential targets for personalized therapies. https://doi.org/10.1080/15376516.2024.2402865

Mechanistic Insights into Di-2-ethylhexyl Phthalate (DEHP)-Induced Metabolic Disruption: Integrating Gut Hormone Secretion and Metabolomics in Colonic Organoids,
Yue, S. Q., Zheng, W. C., Fan, C. B., Wang, C. R., Zhao, Y. N., Yuan, Q. X., Liu, G. T. and Zhao, M. R., *Environmental Science & Technology Letters*, Aug 2024, Vol. 11, no. 9, p. 940-947.

Di-2-ethylhexyl phthalate (DEHP), an endocrine-disrupting plasticizer, may interfere with insulin signaling and increase diabetes risk at low concentrations. Predominantly ingested through food, DEHP directly impacts the intestines where gut hormones that regulate blood sugar are produced. Colonic organoids, with their realistic three-dimensional structure, provide a more physiologically relevant model. Our study used mouse colonic organoids to investigate dietary DEHP exposure on gut endocrine function. Results showed that low doses of DEHP promoted secretion of glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and gastric inhibitory polypeptide (GIP), while decreasing cholecystokinin (CCK) secretion. DEHP exposure increased cyclic AMP levels, supporting the secretion of GLP-1, PYY, and GIP, which may enhance insulin secretion. Metabolomic analyses indicated decreased arachidonic acid levels, potentially increasing inflammation risk and inhibiting gallbladder contraction. These results suggest DEHP exposure significantly alters gut hormone secretion and metabolism, disrupting glucose regulation. Further research is needed to fully understand these mechanisms and their implications for diabetes risk. https://doi.org/10.1021/acs.estlett.4c00593

Interactions of Potential Endocrine-Disrupting Chemicals with Whole Human Proteome Predicted by AlphaFold2 Using an In Silico Approach,
Zhang, F., Tian, Y. W., Pan, Y. T., Sheng, N. and Dai, J. Y., *Environmental Science & Technology*, Sep 2024, Vol. 58, no. 38, p. 16717-16727.

Binding with proteins is a critical molecular initiating event through which environmental pollutants exert toxic effects in humans. Previous studies have been limited by the availability of three-dimensional (3D) protein structures and have focused on only a small set of environmental contaminants. Using the highly accurate 3D protein structure predicted by AlphaFold2, this study explored over 60 million interactions obtained through molecular docking between 20,503 human proteins and 1251 potential endocrine-disrupting chemicals. A total of 66,613,773 docking results were obtained, 1.2% of which were considered to be high binding, as their docking scores were lower than -7. Monocyte to macrophage differentiation factor 2 (MMD2) was predicted to interact with the highest number of environmental pollutants (526), with polychlorinated biphenyls and polychlorinated dibenzofurans accounting for a significant proportion. Dimension reduction and clustering analysis revealed distinct protein profiles characterized by high binding affinities for perfluoroalkyl and polyfluoroalkyl substances (PFAS), phthalate-like chemicals, and other pollutants, consistent with their uniquely enriched pathways. Further structural analysis indicated that binding pockets with a high proportion of charged amino acid residues, relatively low alpha-helix content, and high beta-sheet content were more likely to bind to PFAS than others. This study provides insights into the toxicity pathways of various pollutants impacting human health and offers novel perspectives for the establishment and expansion of adverse outcome pathway-based models. https://doi.org/10.1021/acs.est.4c03774

Mono-2-ethylhexyl phthalate-induced downregulation of MMP11 in foreskin fibroblasts contributes to the pathogenesis of hypospadias,
Zhang, Y. T., Jia, H. X., Fan, J. M., Wang, J., Liu, J. F., Yang, C. H. and Guan, Y., *Ecotoxicology and Environmental Safety*, Oct 2024, Vol. 284.

Hypospadias is one of the most common congenital anomalies of the male urogenital system, and di(2ethylhexyl) phthalate (DEHP), a widely used endocrine-disrupting chemical (EDC), is considered a significant risk factor for this condition. Mono-2-ethylhexyl phthalate (MEHP), the toxic active metabolite of DEHP, has been proven to affect penile development and ultimately result in the hypospadias phenotype. However, while it is acknowledged that hypospadias arises from the aberrant development of multiple penile tissues, the specific impact of MEHP on human foreskin tissue development and its underlying molecular mechanisms of action remain unclear. In this study, we constructed an in vitro toxicity assay for MEHP using human foreskin fibroblasts and employed high-throughput RNA sequencing to investigate the molecular mechanisms subserving the defects in cellular function. We subsequently conducted multi-omics data analysis using public databases to analyze key target genes, and identified MMP11 as a chief downstream gene responsible for the effects of MEHP on HFF-1 cell migration. Through molecular docking analysis and molecular biology experiments, we further demonstrated that the nuclear receptor PPAR-gamma was activated upon binding with MEHP, leading to the suppression of MMP11 expression. Additionally, we found that epigenetic modifications induced by MEHP were also involved in its pathogenic effects on hypospadias. Our research highlights the crucial role of impaired cellular proliferation and migration in MEHP-induced hypospadias. We identified the MEHP/PPAR-gamma/ MMP11 pathway as a novel pathogenic mechanism, providing important potential targets for future preventive strategies with respect to hypospadias. https://doi.org/10.1016/j.ecoenv.2024.116988

Méthodes

EURION Methods Table [Data set],
Audouze, K., Van Duursen, M., Holbech, H., Kortenkamp, A., Legler, J., Levonen, A.-L., Moroni, L., & Rüegg, J., *EU Open Research Repository* (octobre 2024),
The EURION Methods table is the collection of test methods developed by the EURION cluster; a collaboration between eight research projects dedicated to provide new testing and screening methods to identify endocrine disrupting chemicals (EDCs), funded under the European Union's Horizon 2020 Research and Innovation programme. The research in EURION focused on four endocrine-related health domains: thyroid hormone system disruption (ATHENA, ERGO, SCREENED), metabolic disorders (EDCMET, GOLIATH, OBERON), developmental neurotoxicity (ENDpoiNTs) and female fertility (FREIA). https://doi.org/10.5281/zenodo.13927681

Metabolic disrupting chemicals in the intestine: the need for biologically relevant models Zebrafish: what can we learn from this small environment-sensitive fish?,
Erradhouani, C., Bortoli, S., Aït-Aïssa, S., Coumoul, X. and Brion, F., *Febs Open Bio*, Sep 2024, Vol. 14, no. 9, p. 1397-1419.

Although the concept of endocrine disruptors first appeared almost 30 years ago, the relatively recent involvement of these substances in the etiology of metabolic pathologies (obesity, diabetes, hepatic steatosis, etc.) has given rise to the concept of Metabolic Disrupting Chemicals (MDCs). Organs such as the liver and adipose tissue have been well studied in the context of metabolic disruption by these substances. The intestine, however, has been relatively unexplored despite its close link with these organs. In vivo models are useful for the study of the effects of MDCs in the intestine and, in addition, allow investigations into interactions with the rest of the organism. In the latter respect, the zebrafish is an animal model which is used increasingly for the characterization of endocrine disruptors and its use as a model for assessing effects on the intestine will, no doubt, expand. This review aims to highlight the importance of the intestine in metabolism and present the zebrafish as a relevant alternative model for investigating the effect of pollutants in the intestine by focusing, in particular, on cytochrome P450 3A (CYP3A), one of the major molecular players in endogenous and MDCs metabolism in the gut. https://doi.org/10.1002/2211-5463.13878

Screening the ToxCast Chemical Libraries for Binding to Transthyretin,
Eytcheson, S. A., Zosel, A. D., Olker, J. H., Hornung, M. W. and Degitz, S. J., *Chemical Research in Toxicology*, Sep 2024, Vol. 37, no. 10, p. 1670-1681.

Transthyretin (TTR) is one of the serum binding proteins responsible for transport of thyroid hormones (TH) to target tissue and for maintaining the balance of available TH. Chemical binding to TTR and subsequent displacement of TH has been identified as an end point in screening chemicals for potential disruption of the thyroid system. To address the lack of data regarding chemicals binding to TTR, we optimized an in vitro assay

utilizing the fluorescent probe 8-anilino-1-napthalenesulfonic acid (ANSA) and the human protein TTR to screen over 1500 chemicals from the U.S. EPA's ToxCast ph1_v2, ph2, and e1k libraries utilizing a tiered approach. Testing of a single high concentration (target 100 mu M) resulted in 888 chemicals with 20% or greater activity based on displacement of ANSA from TTR. Of these, 282 chemicals had activity of 85% or greater and were further tested in 12-point concentration-response with target concentrations ranging from 0.015 to 100 mu M. An EC50 was obtained for 276 of these 301 chemicals. To date, this is the largest set of chemicals screened for binding to TTR. Utilization of this assay is a significant contribution toward expanding the suite of in vitro assays used to identify chemicals with the potential to disrupt thyroid hormone homeostasis. https://doi.org/10.1021/acs.chemrestox.4c00215

Leveraging new approach methodologies: ecotoxicological modelling of endocrine disrupting chemicals to Danio rerio through machine learning and toxicity studies,
Italiya, G. and Subramanian, S., *Toxicology Mechanisms and Methods*, 2024 Sep 2024.

New approach methodologies (NAMs) offer information tailored to the intended application while reducing the use of animals. NAMs aim to develop quantitative structure-activity relationship (QSAR) and quantitive-Read-Across structure-activity relationship (q-RASAR) models to predict and categorize the acute toxicity of known and unknown endocrine-disrupting chemicals (EDCs) against zebrafish. EDCs are a diverse group of toxic substances that disrupt the endocrine system of humans and animals. The q-RASAR model was constructed and verified using validation metrics (R2 = 0.886 and Q2 = 0.814) which found to be more reliable model compare to QSAR model. The substructure fingerprint was well-fitted for the classification model and it was validated using 10-fold average accuracy (Q = 86.88%), specificity (Sp = 88.89%), Matthew's correlation curve (MCC = 0.621) and receiver operating characteristics (ROC = 0.828). The dataset of unknown substances revealed that phenolphthalein (Php) exhibited a significant level of toxicity based on q-RASAR model. The docking and simulation study indicated that the computationally derived important features successfully bound to the target zebrafish sex hormone binding globulin (zfSHBG). The experimental LC50 value of 0.790 mg L-1 was very close to the predicted value of 0.763 mg L-1, which provides high confidence to the developed model. https://doi.org/10.1080/15376516.2024.2400324

Multiplex aptamer cluster detection platform and systems toxicology study for 17(3-estradiol, bisphenol A, and diethylstilbestrol,
Li, N., Ren, C. X., Hu, Q., Wang, B., Yang, Z. Q., Xiao, L. X. and Guan, T. Z., *Food Chemistry*, Jan 2025, Vol. 463.

Intake of 17 beta-estradiol (E2), bisphenol A (BPA), and diethylstilbestrol (DES) from food can contribute to endocrine disorders. Therefore, developing a sensitive method for the simultaneous detection of E2, BPA, and DES and understanding their combined effects on endocrine disruption are crucial. We developed a fluorescence aptasensing platform utilizing DNase I-assisted cyclic enzymatic signal amplification in conjunction with an aptamer/graphene oxide complex. Using PEG 20000 as a surface-blocking agent, the aptasensor achieved ultralow detection limits of 2.643, 0.3039, and 0.6996 for E2, BPA, and DES, respectively. The sensor demonstrated accurate detection in plastic bottled water at spiked levels of 10 and 100 ng/mL. Systems toxicology revealed 30 potential targets for mixture-induced endocrine disruption. Molecular docking showed binding affinities of E2, BPA, and DES for ESR1 of -9.94, -8.29, and -8.98 kcal/mol, respectively. These results highlight the effectiveness of the aptasensor and provide valuable insights into endocrine disruption mechanisms. https://doi.org/10.1016/j.foodchem.2024.141395

Ultrasensitive Electrochemical Biosensor for Rapid Screening of Chemicals with Estrogenic Effect,
Li, R. X., Li, J., Lu, X. B., Meng, F. L. and Chen, J. P., *Biosensors-Basel*, Sep 2024, Vol. 14, no. 9.

Estrogenic chemicals are widely distributed and structurally diverse. They primarily disrupt estrogen-related metabolism in animals or humans by mimicking the agonistic receptor effects of natural estrogens, thereby influencing the transcription of estrogen receptors to regulate their quantity and sensitivity. This disruption of estrogen-related metabolism can lead to estrogen-related effects, posing risks to biological health, emphasizing the urgent need for simple and effective methods to screen compounds with estrogenic effects. Herein, a new electrochemical biological effect biosensor based on human estrogen receptor alpha (hER alpha) is developed, which uses hER alpha as the biorecognition element and employs the electroactive horseradish peroxidase (HRP) labeled 17 beta-estradiol (E2) multifunctional conjugate HRP-E2 as the signal-boosting element and ligand competition agent. Based on the specific ligand-receptor interaction principle between the target and nuclear receptor, by allowing the test compound to compete with HRP-E2 conjugate

for binding to hER alpha and testing the electrocatalytic signal of the conjugate that fails to bind to the hER alpha estrogen receptor, rapid screening and quantitative detection of chemical substances with estrogenic effect have been achieved. The biosensor shows a wide linear range of 40 pM to 40 nM with a detection limit of 17 pM (S/N = 3) for E2, and the detection limit is 2 orders of magnitude better than that of the previously reported sensors. The biosensor based on ligand-receptor binding can not only quantitatively analyze the typical estrogen E2, but also evaluate the relative estrogen effect strength of other estrogen compounds, which has good stability and selectivity. This electrochemical sensing platform displays its promising potential for rapid screening and quantitative detection of chemicals with estrogenic effects. https://doi.org/10.3390/bios14090436

Binding interaction of typical emerging contaminants on Gobiocypris rarus transthyretin: an in vitro and in silico study,
Li, X. Q., Liu, H. H., Zhao, S. S., Watson, P. and Yang, X. H., *Frontiers of Environmental Science & Engineering*, Nov 2024, Vol. 18, no. 11.

Emerging contaminants (ECs) have drawn global concern, and the endocrine disrupting chemicals is one of the highly interested ECs categories. However, numerous ECs lacks the basic information about whether they can disturb the endocrine related biomacromolecules or elicit endocrine related detrimental effects on organism. In this study, the potential binding affinity and underlying binding mechanism between 29 ECs from 7 chemical groups and Gobiocypris rarus transthyretin (CrmTTR) are investigated and probed using in vitro and in silico methods. The experimental results demonstrate that 14 selected ECs (11 disinfection byproducts, 1 pharmaceuticals and personal care product, 1 alkylphenol, 1 perfluoroalkyl and polyfluoroalkyl substance) are potential CrmTTR binders. The CrmTTR binding affinity of three ECs (i.e., 2,6-diiodo-4-nitrophenol (logRP(T-4) = 0.678 +/- 0.198), 2-bromo-6-chloro-4-nitrophenol (logRP(T-4) = 0.399 +/- 0.0908), tetrachloro-1,4-benzoquinone (logRP(T-4) = 0.272 +/- 0.0655)) were higher than that of 3,3 ',5,5 '-tetraiodo-L-thyronine, highlighting that more work should be performed to reveal their potential endocrine related harmful effects on Gobiocypris rarus. Molecular docking results imply that hydrogen bond and hydrophobic interactions are the dominated non-covalent interactions between the active disruptors and CrmTTR. The optimum mechanism-based (for CrmTTR), and high throughput screening (for CrmTTR, little skate-TTR, seabream-TTR, and human-TTR) binary classification models are developed using three machine learning algorithms, and all the models have good classification performance. To facilitate the use of developed high throughput screening models, a tool named "TTR Profiler" is derived, which could be employed to determine whether a given substance is a potential CrmTTR, little skate-TTR, seabream-TTR, or human-TTR disruptor or not. https://doi.org/10.1007/s11783-024-1895-1

Extracellular vesicles as a potential source of biomarkers for endocrine disruptors in MASLD: A short review on the case of DEHP,
Merret, P.-E., Sparfel, L., Lavau, C., Lagadic-Gossmann, D. and Martin-Chouly, C., *Biochimie*, 2024/09/21/ 2024.

Metabolic dysfunction–Associated Steatotic Liver Disease (MASLD) is a chronic disease with increasing prevalence and for which non-invasive biomarkers are needed. Environmental endocrine disruptors (EDs) are known to be involved in the onset and progression of MASLD and assays to monitor their impact on the liver are being developed. Extracellular vesicles (EVs) mediate cell communication and their content reflects the pathophysiological state of the cells from which they are released. They can thus serve as biomarkers of the pathological state of the liver and of exposure to EDs. In this review, we present the relationships between DEHP (Di(2-ethylhexyl) phthalate) and MASLD and highlight the potential of EVs as biomarkers of DEHP exposure and the resulting progression of MASLD. https://doi.org/https://doi.org/10.1016/j.biochi.2024.09.009

Pioneering an effect-based early warning system for hazardous chemicals in the environment,
Niarchos, G., Alygizakis, N., Carere, M., Dulio, V., Engwall, M., Hyötyläinen, T., Kallenborn, R., Karakitsios, S., Karakoltzidis, A., Kärrman, A., Lamoree, M., Larsson, M., Lundqvist, J., Mancini, L., Mottaghipisheh, J., Rostkowski, P., Sarigiannis, D., Vorkamp, K. and Ahrens, L., *Trac-Trends in Analytical Chemistry*, Nov 2024, Vol. 180.

Existing regulatory frameworks often prove inadequate in identifying contaminants of emerging concern (CECs) and determining their impacts on biological systems at an early stage. The establishment of Early Warning Systems (EWSs) for CECs is becoming increasingly relevant for policy-making, aiming to proactively detect chemical hazards and implement effective mitigation measures. Effect-based methodologies, including

bioassays and effect-directed analysis (EDA), offer valuable input to EWSs with a view to pinpointing the relevant toxicity drivers and prioritizing the associated risks. This review evaluates the analytical techniques currently available to assess biological effects, and provides a structured plan for their systematic integration into an EWS for hazardous chemicals in the environment. Key scientific advancements in effect-based approaches and EDA are discussed, underscoring their potential for early detection and management of chemical hazards. Additionally, critical challenges such as data integration and regulatory alignment are addressed, emphasizing the need for continuous improvement of the EWS and the incorporation of analytical advancements to safeguard environmental and public health from emerging chemical threats. https://doi.org/10.1016/j.trac.2024.117901

Prediction of Endocrine-Disrupting Chemicals Related to Estrogen, Androgen, and Thyroid Hormone (EAT) Modalities Using Transcriptomics Data and Machine Learning,
Ollitrault, G., Marzo, M., Roncaglioni, A., Benfenati, E., Mombelli, E. and Taboureau, O., *Toxics*, Aug 2024, Vol. 12, no. 8.

Endocrine-disrupting chemicals (EDCs) are chemicals that can interfere with homeostatic processes. They are a major concern for public health, and they can cause adverse long-term effects such as cancer, intellectual impairment, obesity, diabetes, and male infertility. The endocrine system is a complex machinery, with the estrogen (E), androgen (A), and thyroid hormone (T) modes of action being of major importance. In this context, the availability of in silico models for the rapid detection of hazardous chemicals is an effective contribution to toxicological assessments. We developed Qualitative Gene expression Activity Relationship (QGexAR) models to predict the propensities of chemically induced disruption of EAT modalities. We gathered gene expression profiles from the LINCS database tested on two cell lines, i.e., MCF7 (breast cancer) and A549 (adenocarcinomic human alveolar basal epithelial). We optimized our prediction protocol by testing different feature selection methods and classification algorithms, including CATBoost, XGBoost, Random Forest, SVM, Logistic regression, AutoKeras, TPOT, and deep learning models. For each EAT endpoint, the final prediction was made according to a consensus prediction as a function of the best model obtained for each cell line. With the available data, we were able to develop a predictive model for estrogen receptor and androgen receptor binding and thyroid hormone receptor antagonistic effects with a consensus balanced accuracy on a validation set ranging from 0.725 to 0.840. The importance of each predictive feature was further assessed to identify known genes and suggest new genes potentially involved in the mechanisms of action of EAT perturbation. https://doi.org/10.3390/toxics12080541

Simultaneous Analysis Method for 27 Endocrine Disrupting Chemicals in Human Urine using UPLC-MS/MS,
Park, S., Park, N. Y. and Kho, Y., *Journal of the Korean Chemical Society-Daehan Hwahak Hoe Jee*, Aug 2024, Vol. 68, no. 4, p. 191-198.

Endocrine disrupting chemicals (EDCs) are compounds that come from outside the body and disrupt hormone action within the body's endocrine system. Examples include parabens, benzophenones, bisphenols, and phthalates, which are currently used in a wide range of applications. However, continuous exposure to them can have negative effects on glycemic control, reproduction, metabolism, nervous system development, pregnancy, childbirth, and growth. In this study, human samples (urine) were pretreated using liquid-liquid-extraction to determine the exposure level of EDCs and then analyzed effectively and rapidly by UPLC-MS/MS. In this way, the analytical conditions were established and the reliability of the simultaneous analysis method was evaluated through method validation. The results showed that the accuracy ranged from 75.28 to 122.36% and the precision ranged from 2.16 to 22.74%. The analytical method established in this study can be used as a methodology for future studies to evaluate and monitor the exposure of EDCs in human samples. https://doi.org/10.5012/jkcs.2024.68.4.191

Boosting miniaturization in clinical analysis: determination of bisphenols in human serum and urine by miniaturized stir bar sorptive dispersive microextraction,
Peris-Pastor, G., Lara-Molina, E. E., Benedé, J. L. and Chisvert, A., *Anal Bioanal Chem*, Nov 13 2024.

In this work, a miniaturized and sustainable method for the determination of endocrine-disrupting bisphenols in human serum and urine employing the miniaturized stir bar sorptive dispersive microextraction (mSBSDME) approach has been developed. As bisphenols are conjugated in the human body to their glucorinated and sulfated forms, an enzymolysis employing a commercial mixture of β-glucuronidase and arylsulfatase was carried out prior to the microextraction procedure to determine their total content. A magnetic covalent organic

framework (COF) was employed as the sorbent to carry out the extraction of the analytes from the biological matrixes, showing good extraction performance due to its hydrophobic, π-π, and dipole-dipole interactions with the analytes. As instrumental detection, liquid chromatography-tandem mass spectrometry (LC-MS/MS) was employed to achieve good sensitivity and selectivity. The method was validated for both matrixes, showing good linearity at least up to 100 ng mL(-1), limits of detection in the low ng mL(-1) range, good precision values (relative standard deviations below 15%), and good accuracy (relative recoveries between 80 and 127%). In order to show the applicability of the developed method, five samples from female volunteers were analyzed with the final aim of offering a practical tool for monitoring the female population's exposure to these highly endocrine-disrupting compounds. This new procedure enhances the implementation of miniaturized sample preparation approaches in biological samples for clinical analysis, giving special relevance to the sustainability of the method. https://doi.org/10.1007/s00216-024-05634-w

Personalized mixture toxicity testing: A proof-of-principle in vitro study evaluating the steroidogenic effects of reconstructed contaminant mixtures measured in blood of individual adults, Strand, D., Lundgren, B., Bergdahl, I. A., Martin, J. W. and Karlsson, O., *Environment International*, Oct 2024, Vol. 192.

Chemical risk assessments typically focus on single substances, often overlooking real-world co-exposures to chemical mixtures. Mixture toxicology studies using representative mixtures can reveal potential chemical interactions, but these do not account for the unique chemical profiles that occur in the blood of diverse individuals. Here we used the H295R steroidogenesis assay to screen personalized mixtures of 24 persistent organic pollutants (POPs) for cytotoxicity and endocrine disruption. Each mixture was reconstructed at a human exposure relevant concentration (1x), as well as at 10- and 100-fold higher concentration (10x, 100x) by acoustic liquid handling based on measured blood concentrations in a Swedish cohort. Among the twelve mixtures tested, nine mixtures decreased the cell viability by 4-18%, primarily at the highest concentration. While the median and maximum mixtures based on the whole study population induced no measurable effects on steroidogenesis at any concentration, the personalized mixture from an individual with the lowest total POPs concentration was the only mixture that affected estradiol synthesis (35% increase at the 100x concentration). Mixtures reconstructed from blood levels of three different individuals stimulated testosterone synthesis at the 1x (11-15%) and 10x concentrations (12-16%), but not at the 100x concentration. This proof-of-principle personalized toxicity study illustrates that population-based representative chemical mixtures may not adequately account for the toxicological risks posed to individuals. It highlights the importance of testing a range of real-world mixtures at relevant concentrations to explore potential interactions and non-monotonic effects. Further toxicological studies of personalized contaminant mixtures could improve chemical risk assessment and advance the understanding of human health, as chemical exposome data become increasingly available. https://doi.org/10.1016/j.envint.2024.108991

Applying cell painting in non-tumorigenic breast cells to understand impacts of common chemical exposures, Tapaswi, A., Cemalovic, N., Polemi, K. M., Sexton, J. Z. and Colacino, J. A., *Toxicology in Vitro*, Dec 2024, Vol. 101.

The general population is exposed to many chemicals which have putative, but incompletely understood, links to breast cancer. Cell Painting is a high-content imaging-based in vitro assay that allows for unbiased measurements of concentration-dependent effects of chemical exposures on cellular morphology. We used Cell Painting to measure effects of 16 human exposure relevant chemicals, along with 21 small molecules with known mechanisms of action, in non-tumorigenic mammary epithelial cells, the MCF10A cell line. Using CellProfiler image analysis software, we quantified 3042 morphological features across approximately 1.2 million cells. We used benchmark concentration modeling to identify features both conserved and different across chemicals. Benchmark concentrations were compared to exposure biomarker concentration measurements from the National Health and Nutrition Examination Survey to assess which chemicals induce morphological alterations at human-relevant concentrations. We found significant feature overlaps between chemicals, including similarities between the organochlorine pesticide DDT metabolite p,p'-DDE and an activator of Wnt signaling CHIR99201. We validated these findings by assaying the activation of Wnt, as reflected by translocation of beta-catenin, following p'-p' DDE exposure. Consistent with Wnt signaling activation, low concentration p',p'-DDE (25 nM) significantly enhanced the nuclear translocation of beta-catenin. Overall, these findings highlight the ability of Cell Painting to enhance mode-of-action studies for toxicants which are common in our environment but incompletely characterized with respect to breast cancer risk. https://doi.org/10.1016/j.tiv.2024.105935

Agenda, actualité, politique et évaluation de l'exposition

4th International Congress on PFAS (Management of environmental and health risks),
(4 février 2025),
Ce congrés est organisé le 4 février 2025 au centre des congrés de Milan (Italie). https://www.webs-event.com/fr/event/PFAS_Italy/programme

Replay webinaire : "Introduction to ECHA's guidance on new CLP hazard classes".
(*Ce webinaire donne un aperçu des nouvelles orientations de l'ECHA sur les classes de danger récemment introduites dans le cadre du règlement sur la classification, l'étiquetage et l'emballage (CLP) : les perturbateurs endocriniens, les propriétés persistantes, bioaccumulables et toxiques ou très persistantes, très bioaccumulatives (PBT/vPvB) et persistantes, mobiles et toxiques ou très persistantes, très mobiles (PMT/vPvM). Au cours du webinaire, sont abordés les objectifs de protection et les critères de classification des nouvelles classes de danger, ainsi que l'élaboration des directives CLP associées. Sont expliqués également les délais réglementaires et la manière dont l'ECHA gère le processus administratif associé une fois que les propositions de classification et d'étiquetage harmonisés sont soumises.*
Le replay ainsi que les présentations sont disponibles. https://echa.europa.eu/fr/-/introduction-to-echa-s-guidance-on-new-clp-hazard-classes#msdynttrid=h4QFlQZNF52iJADElkFh9nPQFUYCEuU7WKd5VnLt4WU

Ajout du triphenyl phosphate dans la liste des substances extrêmement préoccupantes candidates en vue d'une autorisation en raison de ses propriétés de perturbation endocrinienne pour l'environnement.,
ECHA (novembre 2024),
In its October meeting, the Member State Committee agreed to identify triphenyl phosphate as a substance of very high concern because of its endocrine disrupting properties in the environment. The substance will be added to the Candidate List in early November 2024. *https://echa.europa.eu/fr/candidate-list-table*
https://echa.europa.eu/documents/10162/66428151/minutes_msc-87_en.pdf/e1d12c0e-06f3-1280-4a24-e017c641e9dd?t=1728889354977

Deliverable Report. D7.6 Guidance document on extrapolation of thyroid hormone system disruption effects across vertebrate classes,
ERGO (juillet 2024),
In this deliverable, we summarize the most advanced endpoints and assays developed in ERGO. Based on an analysis of the taxonomic applicability across vertebrate classes of MIEs and AOs in the THSD AOP network, we discuss the relevance and potential of these endpoints for cross-species extrapolation. This guidance is developed with a focus on EU regulatory identification of endocrine disrupting compounds. It is mainly intended to inform stakeholders on the advances made by ERGO and their potential regulatory use.
https://ergo-project.eu/wp-content/uploads/2024/08/D7.6-Guidance-document-on-extrapolation-of-thyroid-hormone-system.pdf

Endocrine disruption for the environment recommended for Dibutyl phthalate authorisation entry.,
ECHA (novembre 2024),
Dibutyl phthalate (DBP) (EC 201-557-4, CAS 84-74-2) has been additionally identified as a substance of very high concern due to its endocrine disrupting properties for the environment. The Candidate List entry for DBP has already been amended and we have now sent a recommendation to the European Commission for amending the corresponding REACH authorisation list entry (Annex XIV).
https://echa.europa.eu/fr/recommendations-for-inclusion-in-the-authorisation-list/-/dislist/details/0b0236e1807e09fa#msdynttrid=NIHktebBPTQburmFXCOCwUcAN3E_XX94q6GJMMc42T0

Evaluating results of endocrine and developmental immunotoxicity investigations in extended one_generation reproductive toxicity studies. Final report of the satellite projects originating from the EOGRTS review project,

ECHA (octobre 2024),
The final report of the EOGRTS review project was published in March 2023 and concluded that the EOGRT studies have proven effective in identifying substances of concern. The studies help to clarify if a substance has adverse effects on sexual function, fertility, and development. The results can be used for classifying substances or supporting the identification of endocrine disruptors and protecting parents and their offspring against the unwanted effects of these chemicals. To optimise the design, conduct, analysis, and reporting of future EOGRT studies, ECHA has provided several recommendations of good practices for test laboratories and registrants. Specific important investigations of the EOGRTS have been further analysed by ECHA and Member State experts in so-called satellite projects. These include thyroid system hormone measurements, nipple/areola retention, anogenital distance (AGD), follicle and corpora lutea (CL) count, and the T-cell dependent antibody response (TDAR) assay. This final report provides brief overviews of the objectives and results of these satellite projects1, and their recommendations to improve the design, conduct, analysis, and reporting of these investigations. This report supplements the final report of the EOGRTS review project. https://echa.europa.eu/documents/10162/17228/report_satellite_eogrts_projects_en.pdf/c59ac4ce-7a2c-38df-e9d1-799be95859c7#msdynttrid=oYEI1vrcC31p9N0gsGMHVXwHt0EnUivp2wDth1oS858

HEAL webinar: Endocrine disruptors and women's health, novembre 2024.

A recording of our latest webinar on the impact of endocrine disrupting chemicals on women's reproductive health is now available. https://www.env-health.org/heal-webinar-endocrine-disruptors-and-womens-health/

L'ECHA et cinq pays européens publient une mise à jour sur les progrès réalisés concernant la restriction des PFAS,
ECHA (novembre 2024),
L'Agence européenne des produits chimiques (ECHA) et les autorités du Danemark, de l'Allemagne, des Pays-Bas, de la Norvège et de la Suède ont publié une mise à jour sur l'état d'avancement du processus de restriction des substances perfluoroalkylées et polyfluoroalkylées (PFAS) en Europe. https://echa.europa.eu/fr/-/echa-and-five-european-countries-issue-progress-update-on-pfas-restriction#msdynttrid=p8VWHjwY1-o4BGQmpBy4gaMJ9bnuv2qeafOi8JucAdo

Mise à jour des directives sur les nouveaux critères CLP,
ECHA (novembre 2024),
Mise à jour des directives sur l'application du règlement sur la classification, l'étiquetage et l'emballage (CLP). Cela comprend des conseils sur les nouveaux critères de danger pour perturbateurs endocriniens (PE) pour la santé humaine ou l'environnement ; persistants, bioaccumulables et toxiques (PBT) ; substances très persistantes et très bioaccumulatives (vPvB) ; et persistantes, mobiles et toxiques (PMT) ; substances très persistantes et très mobiles (vPvM). Le document d'orientation sur les perturbateurs endocriniens a été élaboré en collaboration avec l'Autorité européenne de sécurité des aliments (EFSA). https://echa.europa.eu/fr/guidance-documents/guidance-on-clp#msdynttrid=vIO2vSfHRoxUPCss8OlC9_RHoyKeeZgQS08hL7WkfOM

A series of institutional video to inform on Endocrine Disruption research | Improving identification of endocrine disruptors,
Eurion (septembre 2024),
The OBERON project aimed to develop an integrated testing strategy to identifiy the impact of EDCs on metabolic diseases such as obesity, type II diabetes, or liver steatosis. The project combined knowledge from epidemiological studies, advanced in silico computational models predicting the biological activity of substances from their chemical structure and properties, with experimental methods using in vitro tissue cultures and early developmental stages of fish in vivo. This approach was supported by systems biology tools and omics technologies, which mapped changes in gene expression and metabolic pathways imputable to endocrine disruptors (EDCs). Within the EURION cluster as well as within the project, a gigantic number of results were obtained. That is why the OBERON communication team made the attempt to summarize and select some of those results and showcase them in a series of institutional videos. In these videos, the coordinator, work package leaders and principal investigators of the project are interviewed and share their views and findings according the state of their research. Dive into the journey with the complete video on YouTube, or follow the series with social media LinkedIn and Instagram. https://eurion-cluster.eu/a-series-of-institutional-video-to-inform-on-endocrine-disruption-research/

Seven priorities to protect people and environment from endocrine-disrupting chemicals,
(novembre 2024),
As the 2024-2029 EU policy cycle approaches, the EDC-Free Europe coalition is urging EU leaders to prioritise protecting people from the dangers of endocrine-disrupting chemicals (EDCs). In a new statement, the coalition outlines key actions needed to ensure the EU regulatory framework reflects the latest science and tackles the urgent need to reduce—and ultimately eliminate—EDC exposure. https://www.edc-free-europe.org/articles/position-paper/seven-priorities-to-protect-people-and-environment-from-endocrine-disrupting-chemicals

Swiss Symposium on Endocrine Disrupting Chemicals | Food Packaging Forum, octobre 2024.

On October 28, 2024, the Food Packaging Forum, in collaboration with ETH Zürich, held the first Swiss Symposium on Endocrine Disrupting Chemicals (EDCs). The event featured in-depth scientific talks and discussions all about EDCs. Recordings of all talks are available. https://foodpackagingforum.org/events/swiss-symposium-on-endocrine-disrupting-chemicals

Portail des financements et des appels d'ofres de l'UE - Projet financé par l'UE - Projet NeXED : Réseau d'évaluation interdisciplinaire des perturbateurs endocriniens : formation de la prochaine génération de toxicologues,
(de 2025 à 2028),
L'UE a signalé des perturbateurs endocriniens (PE), qui interfèrent avec la fonction hormonale normale, entraînant des effets néfastes sur la santé, particulièrement préoccupants. Dans le cadre des différents programmes réglementaires de l'UE, l'évaluation des perturbateurs endocriniens a récemment considérablement changé et continue d'évoluer rapidement. Des progrès dans les méthodes d'essai pour l'évaluation des perturbateurs endocriniens sont nécessaires pour répondre à ces exigences réglementaires changeantes, et une nouvelle génération de toxicologues doit être formée pour soutenir la mise en œuvre des approches les plus avancées. NeXED s'attaquera à trois défis critiques dans ce domaine. Tout d'abord, l'évaluation des perturbateurs endocriniens humains et environnementaux a toujours été des disciplines distinctes, alors qu'il est de plus en plus nécessaire d'utiliser les données de toutes les espèces dans le cadre d'une approche « Une seule santé ». Deuxièmement, l'évaluation des perturbateurs endocriniens porte actuellement sur des composés uniques, alors que dans un scénario réaliste sur le plan environnemental, les organismes sont confrontés à des mélanges complexes de perturbateurs endocriniens. Troisièmement, de nouvelles méthodes d'essai pour l'évaluation des PE sont nécessaires, couvrant des mécanismes et des effets moins bien caractérisés. NeXED vise à faciliter un changement de paradigme dans l'évaluation des PE en formant une nouvelle génération de toxicologues interdisciplinaires spécialisés dans l'utilisation d'approches harmonisées dans le cadre d'une seule santé. NeXED formera ses 15 doctorants par le biais de recherches, de détachements et d'événements de formation dans le cadre d'un programme de formation interdisciplinaire et intersectoriel. NeXED rassemble 9 bénéficiaires et 11 partenaires associés de 10 pays, en s'appuyant sur des collaborations de longue date dans le cadre de projets existants, notamment les projets EURION Horizon 2020 et le partenariat Horizon Europe sur l'évaluation des risques liés aux produits chimiques (PARC). Le consortium comprend des chercheurs de premier plan issus d'institutions dotées d'excellents programmes de formation doctorale, tous experts en évaluation des PE, ainsi que des partenaires industriels, des organismes de réglementation, des PME et des cabinets de conseil. Grâce à ses expertises complémentaires, le consortium est idéalement placé pour former la génération NeXED de toxicologues. https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/projects-details/43108390/101168892/HORIZON

PRICABASE : un outil pour approfondir le risque chimique dans l'aéronautique,
Argiles, G., Holeckova, I. and Estienny-Bousquet, V., *Archives des Maladies Professionnelles et de l'Environnement*, 2024/05/01, Vol. 85, no. 2, p. 102205.

Résumé Les risques liés aux agents chimiques CMR (cancérogènes, mutagènes et toxiques pour la reproduction) et PE (perturbateurs endocriniens) constituent un enjeu majeur pour la santé des travailleurs du secteur de la sous-traitance aéronautique et spatiale. Les entreprises de ce secteur, nombreuses en Occitanie, ont des difficultés à repérer sur leur lieu de travail ces substances préoccupantes et à mettre en place des actions de substitution ou, à défaut, de réduction ou de maîtrise des risques. Depuis 2017, le PRST (plan régional santé travail) Occitanie se mobilise sur ce sujet au sein du groupe de travail PRICA (prévention du risque chimique dans l'aéronautique). Co-piloté par le service de prévention et de santé au travail toulousain Prevaly et la CARSAT Midi-Pyrénées, ce partenariat inclus la DREETS Occitanie ainsi que 6 autres services

de prévention et de santé au travail interentreprises de la région (APREVYA, CSTG32, PRESTAL, SMTI82, SSTMC, SPSTT), 1 association pluridisciplinaire de santé au travail (ASTI) et 3 services de prévention autonomes (AIRBUS, Air France et ERAMET). Le groupe de travail PRICA a développé à l'échelle de la région un outil, appelé la PRICABASE, permettant, d'une part, d'approfondir les résultats des évaluations du risque chimique conduites par les entreprises et, d'autre part, de les restituer de manière synthétique au médecin du travail, à son équipe pluridisciplinaire ainsi qu'à l'employeur. Concrètement, l'utilisation de la PRICABASE suit 3 étapes : la collecte, l'analyse et la restitution des données. Le service de prévention récupère d'abord l'évaluation du risque chimique de l'entreprise. La PRICABASE est capable d'analyser les évaluations des risques provenant de plusieurs outils d'évaluation. La PRICABASE identifie ensuite la totalité des substances CMR et PE contenues dans les produits que ces dernières soient classées par la classification harmonisée du règlement CLP ou auto-classées par les fournisseurs. La PRICABASE édite enfin un contenu servant de base à la réalisation d'un rapport visuel et pédagogique qui détaille les utilisations des substances préoccupantes pour chaque métier de l'aéronautique présent dans l'entreprise. Le médecin du travail peut ainsi adapter son suivi individuel de l'état de santé et l'entreprise peut plus facilement prioriser ses actions de prévention. À terme, l'outil permettra d'identifier les utilisations des substances CMR et PE dans les métiers de l'aéronautique des entreprises d'Occitanie et permettra de prioriser les prochains travaux du groupe PRICA. https://doi.org/10.1016/j.admp.2024.102205

Les perturbateurs endocriniens (PE) : éviction à l'hôpital comme à la maison. Retour d'expérience en établissement de santé,
Beauvy, J., Paradisi-Prieur, L., Martinez, L., Pandraud, I., Yvinec, C., Paepegaey, A. C., Mezzarobba, V., Cornu, E., Juttet, P. and Le Berre, J. P., *Annales d'Endocrinologie*, octobre 2024, Vol. 85, no. 5, p. 437.

Introduction Les PE sont des polluants environnementaux omniprésents qui, de par leur similitude avec nos hormones, peuvent stimuler ou bloquer nos récepteurs hormonaux et engendrer de nombreuses pathologies [1]. La grossesse et l'enfance sont des périodes particulièrement sensibles aux effets néfastes des PE. Dans ce contexte, notre établissement de santé a reçu un financement par l'ARS afin de former le personnel soignant, sensibiliser les patients et évincer au maximum les PE dans notre maternité. Matériel, méthodes, résultats (1) Formation du personnel de l'hôpital et des correspondants libéraux (sage-femmes, généralistes, gynécologues, endocrinologues) : cours, conférences par des experts reconnus ; (2) Sensibilisation des patients : flyers, ateliers d'éducation en santé environnementale, chambres pédagogiques réelle et virtuelle ; (3) Mise en place d'un QR code, pour sensibiliser les femmes enceintes avec diabète gestationnel et réaliser une étude épidémiologique sur l'exposition aux PE ; (4) Réalisation d'un audit de pratiques et diagnostic des produits utilisés pour devenir une maternité saine : label délivré par le réseau Habitat-Santé-Environnement. Analyse en cours de 350 fiches techniques, fiches de données de sécurité et résumé des caractéristiques des médicaments. Exemples de points à améliorer : privilégier les détergents écolabellisés ; retrait des sprays désodorisants. Discussion Les PE ont des effets néfastes de plus en plus démontrés dans la littérature sur notre santé. Il est de notre devoir de sensibiliser les soignants et les patients, face à ce problème de santé publique. https://doi.org/10.1016/j.ando.2024.08.236

Synthèse - Priorisation des effets sanitaires dans le cadre du programme de surveillance en lien avec les perturbateurs endocriniens,
Julien Caudeville, Pauline Morel, Jérôme Naud, Céline Ménard, Sébastien Denys and Barbier, M. L., *Santé publique France* (novembre 2024),
Santé publique France a engagé un travail de priorisation des effets sanitaires liés aux perturbateurs endocriniens, dans le but de cadrer son programme de surveillance au-delà de la sphère reproductive. La méthode de classement des effets à surveiller prioritairement a combiné à la fois les données de la littérature disponibles ainsi que l'avis d'experts et de parties prenantes du champ via la méthode de consultation Delphi.
https://www.jle.com/download/ers-351935-79868-synthese_priorisation_des_effets_sanitaires_dans_le_cadre_du_programme_de_surveillance_en_lien_avec_les_perturbateurs_endocrini-a.pdf

Consensus on the key characteristics of metabolism disruptors,
La Merrill, M. A., Smith, M. T., Mchale, C. M., Heindel, J. J., Atlas, E., Cave, M. C., Collier, D., Guyton, K. Z., Koliwad, S., Nadal, A., Rhodes, C. J., Sargis, R. M., Zeise, L. and Blumberg, B., *Nature Reviews Endocrinology*, 2024/11/29.

Metabolism-disrupting agents (MDAs) are chemical, infectious or physical agents that increase the risk of metabolic disorders. Examples include pharmaceuticals, such as antidepressants, and environmental agents,

such as bisphenol A. Various types of studies can provide evidence to identify MDAs, yet a systematic method is needed to integrate these data to help to identify such hazards. Inspired by work to improve hazard identification of carcinogens using key characteristics (KCs), we developed 12 KCs of MDAs based on our knowledge of processes underlying metabolic diseases and the effects of their causal agents: (1) alters function of the endocrine pancreas; (2) impairs function of adipose tissue; (3) alters nervous system control of metabolic function; (4) promotes insulin resistance; (5) disrupts metabolic signalling pathways; (6) alters development and fate of metabolic cell types; (7) alters energy homeostasis; (8) causes inappropriate nutrient handling and partitioning; (9) promotes chronic inflammation and immune dysregulation in metabolic tissues; (10) disrupts gastrointestinal tract function; (11) induces cellular stress pathways; and (12) disrupts circadian rhythms. In this Consensus Statement, we present the logic that revealed the KCs of MDAs and highlight evidence that supports the identification of KCs. We use chemical, infectious and physical agents as examples to illustrate how the KCs can be used to organize and use mechanistic data to help to identify MDAs. https://doi.org/10.1038/s41574-024-01059-8

Perturbateurs endocriniens - Problématique et perspectives,
Lombard, A., *Ref : TIP112WEB - "Sécurité et gestion des risques"*, 10 juin 2024.

Les perturbateurs endocriniens (PE) agissent sur les sites d'action des hormones. L'exposition à des substances chimiques industrielles ou naturelles présentes dans des produits de consommation courante et l'environnement, ou lors d'activités professionnelles, serait responsable de l'émergence de maladies à caractère hormonale dans la population. Cet article traite de la définition des PE, de leurs mécanismes d'action, des stratégies scientifiques expérimentales actuellement développées pour les caractériser, ainsi que des précautions à prendre pour limiter les expositions aux PE, dans ce contexte d'incertitude scientifique et réglementaire. https://www.techniques-ingenieur.fr/base-documentaire/environnement-securite-th5/risques-chimiques-toxicologie-et-ecotoxicologie-42156210/perturbateurs-endocriniens-se1607/

Avis de l'Anses relatif à l'évaluation du phosphite de tris(4-nonylphényle, ramifié) et sonidentification en tant que substance extrêmement préoccupante (SVHC) dans le cadre de REACH,
Pasquier, J.-U. M., Paule, V., Christophe, M., Fabrizio, P., Karen, B. and Elodie, ANSES, aout 2024.

Le présent avis a pour objet de présenter les conclusions de l'analyse de cette substance évaluée par l'Anses et la proposition d'identification SVHC issue de cette expertise. https://www.anses.fr/fr/system/files/REACH2013REACh0249.pdf

Main factors influencing the perceived health risk of endocrine-disrupting chemicals: A systematic literature review☆,
Pravednikov, A., Perkovic, S. and Lagerkvist, C. J., *Environmental Research*, Dec 2024, Vol. 262.

Endocrine-disrupting chemicals (EDCs) are linked to rising health issues such as infertility, childhood obesity, and asthma. While some research exists on health risk perceptions of EDCs, a comprehensive understanding across different populations and contexts is needed. We performed a systematic literature review, examining 45 articles published between 1985 and 2023, focusing on both the risk perception of EDCs as a whole as well as individual EDCs found in the environment (e.g., pesticides, bisphenol A, and phthalates). We identified four major categories of factors influencing EDC risk perception: sociodemographic factors (with age, gender, race, and education as significant determinants), family-related factors (highlighting increased concerns in households with children), cognitive factors (indicating that increased EDC knowledge generally led to increased risk perception), and psychosocial factors (with trust in institutions, worldviews, and health-related concerns as primary determinants). This review highlights the complex nature of EDC risk perception, shaped by sociodemographic, family, cognitive, and psychosocial factors, essential for policymakers in crafting educational and communication strategies. Future research should expand to cover more EDCs, use representative samples, and explore the influence of psychosocial factors on risk perception more deeply. https://doi.org/10.1016/j.envres.2024.119836

Comment mieux former les cliniciens à la problématique des perturbateurs endocriniens ?,
Sarfati, J. and Lecornet Sokol, E., *Annales d'Endocrinologie*, 2024/10/01/ 2024, Vol. 85, no. 5, p. 410.

Contexte Les médecins cliniciens sont de plus en plus souvent confrontés à des questions des patients en consultation sur les effets des perturbateurs endocriniens (PE). L'État a mis en place en 2021 une deuxième Stratégie nationale sur les perturbateurs endocriniens (SNPE 2), dont l'objectif principal est de réduire

l'exposition de la population aux PE, notamment par la formation des professionnels de santé (PDS). Il existe des formations diplômantes, mais qui nécessitent pour la plupart un investissement important. Objectif Proposer un contenu facile d'accès alliant expertise scientifique et conseils pratiques, à destination des médecins cliniciens, autour des pathologies endocrinologiques. Méthode Réalisation en visioconférence d'interviews auprès d'experts, diffusion de vidéos par réseaux sociaux et par la newsletter de la Fenarediam. Résultats Douze vidéos ont été réalisées sur une année. Les thèmes abordés sont en rapport avec les pathologies courantes vues en consultation d'endocrinologie : fertilité féminine et masculine, puberté, diabète, pathologies de la thyroïde. La plupart contiennent une partie consacrée à des données scientifiques. Toutes proposent des outils permettant de mettre en place de l'éducation des patients, en vue de limiter l'exposition aux perturbateurs endocriniens. Les vidéos ont été vues entre 50 et 343 fois, avec un total de 2016 visionnages. Discussion et conclusion Il s'agit d'une formation innovante sous format court alliant données scientifiques et outils pratiques, que nous aimerions élargir à d'autres thèmes et à un plus large public de PDS. Une évaluation de l'impact de ce programme sur les pratiques est en cours. Source https://www.ecologie.gouv.fr/strategie-nationale-sur-perturbateurs-endocriniens.
https://doi.org/10.1016/j.ando.2024.08.160

Development and child health in a world of synthetic chemicals,
Wager, J. L. and Thompson, J. A., *Pediatric Research*, 2024 Sep 2024.

Pollution is one of today's most significant threats to the developmental potential of children worldwide. Maternal exposure to toxicants can perturb sensitive windows of fetal development, indirectly through promoting antenatal disorders, abnormal placental adaptation, or directly through maternal-fetal transport. Current evidence clearly shows that persistent organic chemicals promote hypertensive disorders of pregnancy, placental abnormalities, and fetal growth restriction, whereas findings are less consistent for phthalates and bisphenols. Prospective birth cohorts strongly support a link between adverse neurodevelopmental outcomes and prenatal exposure to flame retardants and organophosphate pesticides. Emerging evidence reveals a potential association between in utero exposure to bisphenols and childhood behavioral disorders, while childhood metabolic health is more consistently associated with postnatal exposure to phthalates and bisphenols.ImpactSynthesizes emerging evidence linking modern forms of chemical pollution to antenatal disorders, fetal growth restriction and childhood disorders.Highlights potential developmental impacts of emerging pollutants of concern now ubiquitous in our environment but without regulatory restrictions. https://doi.org/10.1038/s41390-024-03547-z

The silent threat and countermeasures: Navigating the mixture risk of endocrine-disrupting chemicals on pregnancy loss in China,
Xu, Y. Q., Wang, T., Yin, J., Hu, L. G. and Liao, C. Y., *Eco-Environment & Health*, Sep 2024, Vol. 3, no. 3, p. 266-270.

Currently, many countries and regions worldwide face the challenge of declining population growth due to persistently low rates of female reproduction. Since 2017, China's birth rate has hit historic lows and continued to decline, with the death rate now equaling the birth rate. Concerns have emerged regarding the potential impact of environmental contaminants on reproductive health, including pregnancy loss. Endocrine-disrupting chemicals (EDCs) like phthalate esters (PAEs), bisphenol A (BPA), triclosan (TCS), and perfluoroalkyl substances (PFASs) have raised attention due to their adverse effects on biological systems. While China's 14th Five-Year Plan (2021-2025) for national economic and social development included the treatment of emerging pollutants, including EDCs, there are currently no national appraisal standards or regulatory frameworks for EDCs and their mixtures. Addressing the risk of EDC mixtures is an urgent matter that needs consideration from China's perspective in the near future. In this Perspective, we delve into the link between EDC mixture exposure and pregnancy loss in China. Our focus areas include establishing a comprehensive national plan targeting reproductive-aged women across diverse urban and rural areas, understanding common EDC combinations in women and their surrounding environment, exploring the relationship between EDCs and pregnancy loss via epidemiology, and reconsidering the safety of EDCs, particularly in mixtures and low-dose scenarios. We envision that this study could aid in creating preventive strategies and interventions to alleviate potential risks induced by EDC exposure during pregnancy in China. https://doi.org/10.1016/j.eehl.2024.03.003

Temporal trends in phthalate metabolite exposure of girls in the United States across sociodemographic factors and intersectional social identities: National Health and Nutrition Examination Survey (NHANES) 2001-2018,

Oskar, S., Mook, J., Smith, M. K., Huang, X. Y. and Mcdonald, J. A., *Environmental Research*, Nov 2024, Vol. 260.

Background: Exposure to phthalates during the pubertal window is linked to an increased risk of chronic diseases. Understanding temporal trends in exposure can inform public health initiatives. Objective: Characterize temporal trends in phthalate metabolite levels in adolescent girls overall and by sociodemographic characteristics. Methods: We used the cross-sectional data from each cycle of NHANES from years 2001-2018. We included participants aged 8-14 years who had at least one urinary measurement of the selected 12 phthalate metabolites within the study period (n = 2063). We used multivariable linear regression to assess temporal trends for selected individual phthalate metabolite concentrations (ng/ml) and source groupings of parent metabolites (sum low and high molecular weight phthalates; ∑LMW and ∑HMW), overall and by sociodemographic characteristics (race/ethnicity), nativity, socioeconomic status (SES), intersection of race/ethnicity-SES) to assess for modification. Results: Overall, levels of ∑HMW and ∑LMW declined between 2001 and 2018; however, only ∑LMW consistently differed by all sociodemographic characteristics. Trends in ∑LMW concentration were significantly higher across all racial/ethnic groups, ranging from an average of 35% (Other Hispanic) to 65% (Mexican American and non-Hispanic Black) higher than non-Hispanic White (all p-values <0.0001). Compared to non-Hispanic White, a significant decrease in MiBP concentrations was observed for non-Hispanic Black (15% decrease beta(Spline) = -0.16, p < 0.0001) and Other Hispanic (28% decrease, beta(Spline) = -0.33, p = 0.01) in 2011-2018 versus 2001-2010. Summary and individual LMW metabolite phthalate concentrations were 11%-49% higher among girls with low vs. high SES. LMW metabolites MBP and MiBP were on average 22% and 35% higher, respectively, among foreign-born vs. U.S.-born girls. Compared to non-Hispanic Whites, all racial/ethnic groups had statistically significant higher trends in ∑LMW concentrations irrespective of SES. Significance: Girls identifying with a historically disadvantaged racial/ethnic groups exhibited elevated ∑LMW concentrations irrespective of SES; suggesting the need for targeted interventions to mitigate exposure among the most historically disadvantaged strata. https://doi.org/10.1016/j.envres.2024.119755

Evaluation of dermal exposure to phthalates and parabens resulting from the use of hair relaxers, Pierce, J. S., Cheatham, D., Campbell, D. A., Lazcano, R. F., Busch, C. E., Miller, E. W. and Beckett, E. M., *International Journal of Environmental Health Research*, 2024 Sep 2024.

Hair relaxers have been suggested as a source of exposure to parabens and phthalates. However, dermally absorbed doses of these chemicals resulting from consumer use of hair relaxers have yet to be quantified, and results from epidemiological studies have consistently demonstrated that there is no increased risk for hormone-sensitive, reproductive cancers associated with use of hair relaxers among Black women. Therefore, dermal absorption of parabens and phthalates associated with hair relaxer use for several commercially available hair relaxer kits was modeled using IH SkinPerm (TM). The chemicals detected in the hair relaxer kits included methylparaben (MP), ethylparaben (EP), butylparaben (BP), diethyl phthalate (DEP), bis(2-ethylhexyl) phthalate (DEHP), and the phthalate substitute bis(2-ethylhexyl) adipate (DEHA). The daily absorbed dose ranges (mg/kg/day), standardized over a year of product use, were as follows: 8.64 x 10-5-0.00116 MP, 2.30 x 10-8-3.07 x 10-6 EP, 3.24 x 10-8-4.33 x 10-6 BP, 8.65 x 10-9-1.15 x 10-6 DEP, and 8.94 x 10-7-0.000119 DEHP for Kit #1; 8.44 x 10-5-0.00113 MP and 7.91 x 10-5-0.00106 DEP for Kit #2; and 2.49 x 10-6-3.33 x 10-5 MP, 1.52 x 10-8-2.03 x 10-6 EP, 3.29 x 10-9-4.39 x 10-7 DEP, and 3.11 x 10-6-4.14 x 10-5 DEHA for Kit #3. These absorbed doses were well below applicable health-based guidance values, indicating consumer exposure from product use is not expected to pose a health risk. These results provide valuable information for health risk evaluations for hair relaxer use. https://doi.org/10.1080/09603123.2024.2402836

Longitudinal Exposomics in a Multiomic Wellness Cohort Reveals Distinctive and Dynamic Environmental Chemical Mixtures in Blood, Sdougkou, K., Papazian, S., Bonnefille, B., Xie, H. Y., Edfors, F., Fagerberg, L., Uhlén, M., Bergström, G., Martin, L. J. and Martin, J. W., *Environmental Science & Technology*, Sep 2024, Vol. 58, no. 37, p. 16302-16315.

Chemical exposomes can now be comprehensively measured in human blood, but knowledge of their variability and longitudinal stability is required for robust application in cohort studies. Here, we applied high-resolution chemical exposomics to plasma of 46 adults, each sampled 6 times over 2 years in a multiomic cohort, resulting in 276 individual exposomes. In addition to quantitative analysis of 83 priority target analytes, we discovered and semiquantified substances that have rarely or never been reported in humans, including personal care products, pesticide transformation products, and polymer additives. Hierarchical cluster analysis

for 519 confidently annotated substances revealed unique and distinctive coexposures, including clustered pesticides, poly(ethylene glycols), chlorinated phenols, or natural substances from tea and coffee; interactive heatmaps were publicly deposited to support open exploration of the complex (meta)data. Intraclass correlation coefficients (ICC) for all annotated substances demonstrated the relatively low stability of the exposome compared to that of proteome, microbiome, and endogenous small molecules. Implications are that the chemical exposome must be measured more frequently than other omics in longitudinal studies and four longitudinal exposure types are defined that can be considered in study design. In this small cohort, mixed-effect models nevertheless revealed significant associations between testosterone and perfluoroalkyl substances, demonstrating great potential for longitudinal exposomics in precision health research. https://doi.org/10.1021/acs.est.4c05235

Toxicité sur les animaux

Vulnerable periods for the mouse mammary gland: Comparison of the effects of ethinyl estradiol exposures during two early stages of development,
Clark, Z. W., Mogus, J. P., Marando, J., Effenson, R. S. and Vandenberg, L. N., *Reproductive Toxicology*, Dec 2024, Vol. 130.

The mammary gland is responsive to endogenous hormones and environmental chemicals that are estrogen receptor (ER) agonists. The mouse mammary gland offers the opportunity to dissect the most sensitive windows of exposure. 17 alpha-ethinyl estradiol (EE2) is a pharmaceutical ER agonist that often serves as a positive control for estrogen-active chemicals. Here, adult female mice were exposed to EE2 starting either at pregnancy day 7, or on lactational day 1, and exposures continued until the litters were weaned. The pups were therefore exposed during gestation + the juvenile period, or during the juvenile period alone. The morphology of the mammary gland was evaluated in both male and female offspring at two life stages: weaning (postnatal day [PND]21) and at puberty (PND32). Other hormone-sensitive outcomes evaluated included body weight, anogenital index, frequency of open vagina, and weight of the uterus. We found age- and sex-dependent effects of EE2 on these estrogenresponsive endpoints including the morphology of the mammary gland. Importantly, EE2 altered mammary gland morphology even when exposures were limited to the juvenile period. However, the number of endpoints that were affected in animals from the EE2-Juvenile-Only period were fewer, and typically of a lower magnitude, compared to those observed in the EE2-Gest-Juvenile group. Understanding the effects of environmental estrogen exposures during the juvenile period is critical because humans are exposed to estrogenic pollutants throughout life, including in early childhood. https://doi.org/10.1016/j.reprotox.2024.108722

Gestational bisphenol A exposure alters energy homeostasis and adult hypothalamic neurogenesis in female mice,
Feighan, K. M., Nesan, D. and Kurrasch, D. M., *Scientific Reports*, Jul 2024, Vol. 14, no. 1.

Regulation of physiological homeostasis, including energy balance, is thought to be modified by low levels of adult neurogenesis in the hypothalamus. Hormones such as oestradiol can influence both embryonic and adult hypothalamic neurogenic programs, demonstrating a sensitivity of hypothalamic neural progenitor cells to endogenous hormones. Previously we showed that gestational exposure to environmental levels of the xenoestrogen bisphenol A (BPA) changed neural progenitor cell behaviors in the embryo; however, we did not examine if these changes were permanent to affect adult neurogenesis. Here we investigated whether adult neuro- and/or gliogenesis were altered in mice prenatally exposed to BPA and placed on a high-fat diet challenge. Gestationally exposed adult female mice on a standard diet gained less weight than non-BPA controls, whereas gestationally exposed BPA females on a high-fat diet gained more weight than controls. Males exposed to gestational BPA showed no differences in weight gain relative to control males. Concomitantly, adult neurogenesis was increased in the VMH, DMH, and PVN of adult female mice exposed to BPA on standard diet, suggesting that disrupted adult neurogenesis might perturb normal energy balance regulation in females. These results add to growing evidence that low-dose BPA exposure in utero causes changes to adult hypothalamic function. https://doi.org/10.1038/s41598-024-66726-2

Neurotoxic effects of perinatal exposure to Bisphenol F on offspring mice,
Huo, S. M., Li, B., Du, J. Y., Zhang, X. L., Song, M. and Li, Y. F., *Environmental Pollution*, Dec 2024, Vol. 362.

Bisphenols constitute a diverse group of endocrine-disrupting chemicals (EDCs) that impact hormone activity. Bisphenol F (BPF) is commonly used as a substitute for Bisphenol A (BPA). The disruption of the immune system by EDCs during embryonic brain development has been suggested as a plausible factor to neurodevelopmental disorders. We investigated the neurotoxic effects of perinatal exposure to BPF on offspring mice. Female mice were exposed to BPF through their drinking water on day 0.5 of pregnancy, and this exposure continued until the offspring mice were weaned, throughout the perinatal period. Our findings revealed that exposure to BPF hindered both growth and neurodevelopment in offspring mice, with a more pronounced effect observed in males. Additionally, transcriptomic analysis was conducted on the brains of male offspring mice exposed to high doses of BPF. In summary, our study indicates that perinatal exposure to BPF results in neurodevelopmental impairments in male offspring mice, linked to oxidative stress, inflammatory responses, and immune dysregulation. These findings underscore that BPF may not be a safe substitute for BPA. Thus, there is a pressing need to reevaluate the current regulation of BPF. https://doi.org/10.1016/j.envpol.2024.124932

Endocrine-Disrupting Effects of Transplacental and Translactational Exposure to Tembotrione on Hormone Status in Wistar Rat Offspring at Different Developmental Stages: A Pilot Study,
Katic, A., Karaconji, I. B., Micek, V. and Zeljezic, D., *Toxics*, Aug 2024, Vol. 12, no. 8.

Green agronomy promotes the implementation of natural and naturally derived substances in crop protection. In the present study, we evaluated the endocrine-disrupting potential of the allelopathic herbicide tembotrione in Wistar rats by studying the hormone status of offspring from the treated dams. Three doses of tembotrione (0.0004, 0.0007, and 4.0 mg/kg b.w./day) have been administered to dams during gestation and/or lactation. In the serum of newborn, weaning, and pubertal female and male offspring, 17 beta-estradiol and testosterone were determined using enzyme-linked immunosorbent assay. A decrease in 17 beta-estradiol and testosterone was observed in female and male weaning and pubertal offspring exposed to all doses of tembotrione during gestation and lactation. In weaning offspring exposed only during lactation, 17 beta-estradiol dropped significantly after exposure to the two lower doses and testosterone after exposure to the lowest dose of tembotrione. The greatest effect was observed at the lowest dose of tembotrione. In newborns, we observed increased 17 beta-estradiol after exposure to two lower doses of tembotrione and significantly increased testosterone after exposure to the lowest dose. The highest dose of tembotrione decreased 17 beta-estradiol significantly in newborn females. The obtained results suggest that tembotrione might be considered a pro-estrogenic or estrogen agonistic compound under the exposure conditions applied in this investigation. https://doi.org/10.3390/toxics12080533

Effects of maternal nonylphenol exposure on the proliferation of glial cells in the brain of male offspring mice,
Lee, S. H., Shin, H. S., So, Y. H., Lee, D. H., Kim, J. Y., Lee, E. H. and Jung, E. M., *Animal Cells and Systems*, Dec 2024, Vol. 28, no. 1, p. 439-452.

Glial cells play a significant role in maintaining brain homeostasis and normal brain development, and their functions can be impaired by exposure to endocrine disruptors. 4-n-Nonylphenol (NP), a representative endocrine disruptor, is widely used in personal care products and industrial materials. NP accumulates in various organs, including the brain, of living organisms and adversely influences brain health. However, studies on the effects of NP on glial cells are limited. This study aims to investigate the effects of NP on glial cells using primary mixed glial cells and offspring mice exposed to NP during gestation and lactation. In vitro experiments revealed that NP exposure stimulated the astrocytes and microglia proliferation but not oligodendrocytes. NP exposure activated microglia and reduced myelin protein expression in oligodendrocytes. Moreover, maternal NP exposure increased the numbers of microglia and oligodendrocytes in the cerebral cortex of adult offspring. NP exposure caused anxiety- and depressive-like behaviors in adult mice. Collectively, these findings suggest that maternal NP exposure negatively affects the brain development in adult offspring mice. https://doi.org/10.1080/19768354.2024.2401389

Prenatal exposure to dibutyl phthalate contributes to erectile dysfunction in offspring male rats by activating the RhoA/ROCK signalling pathway,
Liu, S. Y., Li, J. Y., Wang, W. H., Zhang, Y. J., Li, S. F., Li, T. W., Jiang, J. T. and Zhao, F. J., *Toxicology*, Nov 2024, Vol. 508.

Prenatal exposure to dibutyl phthalate (DBP) has been reported to cause erectile dysfunction (ED) in adult offspring rats. However, its underlying mechanisms are not fully understood. Previously, we found that DBP activates the RhoA/ROCK pathway in the male reproductive system. This study investigated how prenatal exposure to DBP activates the RhoA/ROCK signalling pathway, leading to ED in male rat offspring. Pregnant rats were stratified into DBP-exposed and NC groups, with the exposed group receiving 750 milligrams per kilogram per day (mg/kg/day) of DBP through gavage from days 14-18 of gestation. DBP exposure activated the RhoA/ ROCK pathway in the penile corpus cavernosum (CC) of descendants, causing smooth muscle cell contraction, fibrosis, and apoptosis, all of which contribute to ED. In vitro experiments confirmed that DBP induces apoptosis and RhoA/ROCK pathway activation in CC smooth muscle cells. Treatment of DBP-exposed offspring with the ROCK inhibitor Y-27632 for 8 weeks significantly improved smooth muscle cell condition, erectile function, and reduced fibrosis. Thus, prenatal DBP exposure induces ED in offspring through RhoA/ROCK pathway activation, and the ROCK inhibitor Y-27632 shows potential as an effective treatment for DBP-induced ED. https://doi.org/10.1016/j.tox.2024.153925

Une exposition développementale combinée à un déséquilibre alimentaire et à un perturbateur endocrinien induit des lésions prostatiques chroniques : mécanismes d'action,
Mauduit, C., Gharieb, K., Doumandji, N., Bellon, R. P., Inoubli, L., Siddeek, B., Decaussin-Petrucci, M., Traverse-Glehen, A. and Benahmed, M., *Morphologie*, 2024/12/01/ 2024, Vol. 108, no. 363, Supplement, p. 100872.

Le cancer de la prostate a des facteurs de risques à la fois hormonaux et nutritionnels [1]. Plusieurs études suggèrent une association positive entre l'obésité et le risque de cancer de la prostate, en particulier les formes agressives de la maladie [2], [3]. Cependant, les mécanismes ne sont pas encore entièrement compris. Notre objectif était d'examiner les effets combinés de l'exposition, pendant le développement précoce, à un régime alimentaire riche en matières grasses (RRG) et à un xénœstrogène (Estradiol benzoate, EB) sur la prostate adulte. Pour cela, des rats sont exposés pendant la gestation et jusqu'à leur sevrage à un RRG (60 % de matières grasses) ou à un régime normal. À la naissance, les rats mâles sont alors exposés ou non à l'EB, du jour 1 au jour 5 après la naissance. Les rats sont sacrifiés à l'âge adulte. Ce protocole définit 4 groupes : témoin (régime normal, non exposé à l'EB) ; exposé uniquement au RRG ; exposé uniquement à l'EB ; exposé aux deux facteurs de risque (RRG+EB). Nos résultats montrent que les rats exposés à la fois à un RRG et à l'EB présentent des lésions de la prostate plus importantes que les rats exposés uniquement à l'un ou l'autre facteur de risque. Ces lésions sont une augmentation de la taille de la prostate, une hyperplasie des cellules épithéliales et un nombre élevé de foyers inflammatoires. Ces rats présentent également des niveaux plus élevés des cytokines pro-inflammatoires TNFa, IL6 et CCL2/MCP1 et une activation accrue de l'inflammasome (NLRP3). En conclusion, ces résultats suggèrent qu'une exposition combinée à un déséquilibre alimentaire et à des xénoestrogènes pendant le développement précoce peuvent avoir des effets durables, augmenter le risque d'inflammation chronique de la prostate à l'âge adulte, facteur de risque du cancer de la prostate [4], [5]. https://doi.org/https://doi.org/10.1016/j.morpho.2024.100872

Pesticide-induced transgenerational alterations of genome-wide DNA methylation patterns in the pancreas of Xenopus tropicalis correlate with metabolic phenotypes,
Roza, M., Eriksson, A. N. M., Svanholm, S., Berg, C. and Karlsson, O., *Journal of Hazardous Materials*, Oct 2024, Vol. 478.

The unsustainable use of manmade chemicals poses significant threats to biodiversity and human health. Emerging evidence highlights the potential of certain chemicals to cause transgenerational impacts on metabolic health. Here, we investigate male transmitted epigenetic transgenerational effects of the anti-androgenic herbicide linuron in the pancreas of Xenopus tropicalis frogs, and their association with metabolic phenotypes. Reduced representation bisulfite sequencing (RRBS) was used to assess genome-wide DNA methylation patterns in the pancreas of adult male F2 generation ancestrally exposed to environmentally relevant linuron levels (44 +/- 4.7 mu g/L). We identified 1117 differentially methylated regions (DMRs) distributed across the X. tropicalis genome, revealing potential regulatory mechanisms underlying metabolic disturbances. DMRs were identified in genes crucial for pancreatic function, including calcium signalling (clstn2, cacna1d and cadps2), genes associated with type 2 diabetes (tcf7l2 and adcy5) and a biomarker for pancreatic ductal adenocarcinoma (plec). Correlation analysis revealed associations between DNA methylation levels in these genes and metabolic phenotypes, indicating epigenetic regulation of glucose metabolism. Moreover, differential methylation in genes related to histone modifications suggests alterations in the epigenetic machinery. These findings underscore the long-term consequences of environmental

contamination on pancreatic function and raise concerns about the health risks associated with transgenerational effects of pesticides. https://doi.org/10.1016/j.jhazmat.2024.135455

Sex-specific effects on elements of the social brain neural network in Wistar rats from perinatal exposure to FireMaster 550 or its components,
Schkoda, S., Horman, B., Witchey, S., Armour, G. S., Nelson, M., Gaeta, E., Scott, M. and Patisaul, H. B., *Neurotoxicology*, Dec 2024, Vol. 105, p. 111-120.

Developmental exposure to chemical flame retardants (FRs) has been linked to a variety of neurodevelopmental disorders and abnormal socioemotional behaviors in human and laboratory animal studies. We have previously shown in Wistar rats that gestational and lactational exposure to the FR mixture Firemaster 550 (FM 550) or its brominated or organophosphate ester (OPFR) components (at 2000 mu g, 1000 mu g, and 1000 mu g oral to the dam respectively (absolute and not by bodyweight)) results in increased anxiety-like behaviors in females and decreased sociality in both sexes. Using their siblings, this study characterized sex and chemical specific targets of disruption in brain regions underlying each behavioral phenotype. Offspring were exposed across gestation and lactation then prepared for either immunohistochemistry or autoradiography at postnatal day 90 to quantify expression of serotonin, estrogen receptor alpha (ER alpha), and oxytocin receptor (OTR) in multiple brain regions. No effect of exposure was found in males for any biological target. In females, serotonin innervation was increased in the medial amygdala of FM 550 exposed animals while ER alpha expression in the bed nucleus of the stria terminalis (BNST) was reduced by FM 550 and OPFR. Evidence of disrupted OTR was observed in males, particularly the BNST but considered an exploratory finding given the small sample size. These results begin to shed light on the mechanisms by which developmental FR exposure alters socioemotional behaviors of relevance to neurodevelopmental disorders. https://doi.org/10.1016/j.neuro.2024.09.001

Higher Sensitivity of Rat Testes to Nano Nickel than Micro Nickel Particles: A Toxicological Evaluation,
Singh, M., Verma, Y. and Rana, S. V. S., *Reproductive Sciences*, Nov 2024, Vol. 31, no. 11, p. 3521-3531.

Present investigations were undertaken to record the vulnerability of testis to nickel oxide nano and microparticles in Wistar rat with special reference to their preferred bioaccumulation, consequent generation of reactive species, reciprocal influence on testosterone synthesis, DNA damage in spermatids and histopathological changes. Suitable numbers of rats were gavaged NiONPs or NiOMPs (5 mg/kg b.w.each) for 15 and 30 days. Testes en bloc were removed and processed for the estimation of selected parameters. Results showed that rat testes could accumulate nickel in an exposure time dependent manner. Generation of malondialdehyde, a denominator of ROS, increased significantly in the testes of NiONPs treated rats. Moreover, serum testosterone values also increased in NiONPs treated rats. Higher DNA damage in sperms was also recorded. Nano and microparticles of nickel, both could induce specific dose and time dependent lesions in the testis of rat. Histopathological results revealed degeneration of germinal epithelium and spermatocytes; hypertrophy of seminiferous tubules and necrosis. SEM results also indicated specific morphological changes in cellular components of tubules. This study suggests that testis is also vulnerable to the adverse effects of NiONPs alike liver and kidney. Both micro and nanoparticles of nickel elicited differential effects in a dose and exposure time dependent manner. However, NiONPs induced greater overall toxicity than NiOMPs. The results are expected to be helpful in determining the human reproductive health risks, associated with environmental/ occupational exposure to nanoparticles of nickel. https://doi.org/10.1007/s43032-024-01694-6

Minor changes to circulating steroid hormones in female rats after perinatal exposure to diethylstilbestrol or ketoconazole,
Vazakidou, P., Bouftas, N., Heinzelmann, M., Johansson, H. K. L., Svingen, T., Leonards, P. E. G. and Van Duursen, M. B. M., *Reproductive Toxicology*, 2024/12/01/ 2024, Vol. 130, p. 108726.

Current chemical test strategies lack sensitive markers for detecting female reproductive toxicity caused by endocrine disrupting chemicals (EDCs). In search of a potentially sensitive readout, the steroidogenic disrupting effects of the well-known EDCs ketoconazole (KTZ) and diethylstilbestrol (DES) were investigated in vitro and on circulating steroid hormones in perinatally exposed female Sprague-Dawley rats. Twenty-one steroid hormones were analysed using LC-MS/MS in plasma from female rat offspring at postnatal day (PD) 6, 14, 22, 42 and 90. Most circulating steroid hormone levels increased with age except for estrone (E1), estradiol (E2) and backdoor pathway androsterone (ANDROST), which decreased after PD 22. Perinatal exposure to DES did not affect circulating steroid hormone levels at any dose or age compared to controls.

KTZ exposure resulted in dose-dependent increase of corticosterone (CORTICO) at PD 6 and PD 14, with statistical significance only at PD 14. In the in vitro gold standard H295R steroidogenesis assay, twenty-one steroid hormones were measured instead of only T and E2. DES had subtle effects on steroidogenesis, whereas KTZ decreased most steroid hormones, but increased CORTICO, progesterone (P4), estriol (E3) initially (around 0.1–1 μM) before decreasing. Our data suggests that circulating steroidomic profiling may not be a sensitive readout for EDC-induced female reproductive toxicity. Further studies are needed to associate H295R assay steroidomic profiles with in vivo profiles, especially in target tissues such as adrenals or gonads. Expanding the H295R steroidogenic assay to include a comprehensive steroidomic profile may enhance its regulatory applicability. https://doi.org/https://doi.org/10.1016/j.reprotox.2024.108726

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